

Australia

Patents Act 1990

IN THE MATTER OF Australian
Patent Application Serial No. 696764 by
Human Genome Sciences, Inc

and

IN THE MATTER OF Opposition
thereto by Ludwig Institute for Cancer
Research.

STATUTORY DECLARATION

I, Peter Adrian Walton Rogers of the Department of Obstetrics and Gynaecology, Monash University, Clayton, Victoria, Australia do solemnly and sincerely declare as follows:

INTRODUCTION

- 1.1 I have been asked by the Ludwig Institute for Cancer Research ("Ludwig Institute") to serve as a scientific expert in connection with Ludwig Institute's opposition to the issuance of a patent to Human Genome Sciences, Inc., ("HGS") based on HGS's Australian Patent Application No. 696764. The patent application relates generally to a gene and protein for an alleged novel vascular endothelial growth factor called "Vascular Endothelial Growth Factor 2" ("VEGF2"), and thus pertains to an area of biology closely related to my research and expertise. I understand that Ludwig Institute is a named co-applicant for a different patent application directed to subject matter that may be related to "VEGF2."
- 1.2 In February 2000 I executed a first statutory declaration to provide evidence in support of Ludwig Institute's opposition, hereinafter referred to as "OPR1" (Opponents, Peter Rogers, 1st Declaration). That first declaration included a brief summary of my scientific credentials and an introduction in which I set forth some

conventional terminology that I used throughout the declaration. I shall continue to use such terminology herein.

- 1.3 I hereby reaffirm my understanding that I have an overriding duty to the Patent Office (and to any Australian Federal Court that should review the Patent Office decision) to provide objective scientific analysis that I believe to be truthful. I hereby affirm that, to the best of my knowledge and belief, factual statements herein are true and opinion statements herein represent my objective scientific opinion and analysis.
- 1.4 My original declaration included evidence relevant to whether the opposed application lacked novelty (OPR1 at 2.1-2.8); lacked inventive step (OPR1 at 3.1-3.8); lacked sufficiency (OPR1 at 4.1-4.14); lacked fair basis (OPR1 at 5.1-5.12); lacked clarity (OPR1 at 6.1-6.11); and was not a manner of manufacture (OPR1 at 7.1-7.6). In response, the patent applicant HGS filed declarations from six scientists, John Stanley Mattick (hereinafter "AJM1" (Applicants, John Mattick, 1st Declaration)), Jennifer Ruth Gamble ("AJG1"), Nicholas Kim Hayward ("ANH1"); Thomas Rapoport ("ATR1"), Stuart Aaronsson ("ASA1"), and Susan Power ("ASP1"). In this declaration I respond to issues raised by the HGS declarants.
- 1.5 For the most part, the six HGS declarations are not organized by grounds of opposition, and it is not always possible to determine the issues to which the HGS declarants are responding. The HGS declarations also are repetitive of each other. I have tried to determine the issues to which HGS's evidence pertains, and reply to those issues in a topical fashion, rather than addressing each declaration serially. I have attempted to organize many of my comments in the same manner as my original OPR1 declaration, where it appears that HGS's evidence is addressing particular patent issues (e.g., novelty-inventive step or lack of fair basis/insufficiency). I have also addressed particular issues raised by individual declarants. Failure to address any specific issues should not be interpreted as agreement with any HGS declarant.

- 1.6 Unless I specifically state otherwise below, I affirm the facts and opinions expressed in my prior declaration. Nothing in HGS's evidence-in-answer causes me to change the opinions embodied in my first declaration.

PRELIMINARY REMARKS REGARDING QUALITY OF HGS EVIDENCE

- 2.1 I would first like to make the following preliminary observations about the HGS evidence-in-answer which are relevant to most or all patentability issues.
- A. THE HGS DECLARATIONS APPLY A SCIENTIFIC "DOUBLE STANDARD"
- 2.2 I have reviewed all of the declarations filed by HGS and observe that the declarants that reviewed Professor Alitalo's declaration (filed as part of Ludwig Institute's evidence-in-opposition) seem to believe that no conclusions can be drawn from a scientific experiment unless the experiment contains absolutely perfect, parallel positive and negative controls. (See AJG1 at 7.43 and 7.52; ANH1 at 5.6-5.13; ASA1 at 11, 13, 14, and 18] The Alitalo declaration provided direct evidence that VEGF2 cannot be expressed and secreted in the manner taught by HGS in the opposed application, but the HGS declarants suggest that such experiments are flawed and cannot form the basis for any valid conclusions.
- 2.3 The HGS declarants also are very restrictive of the conclusions that they are willing to draw based upon prior art. For example, when discussing the prior art, Dr. Mattick does not believe that any conclusions can be drawn about whether antibodies raised against a prior art VEGF polypeptide will cross react with *identical* sequences that occur in VEGF2 on a theoretical level - he would need actual experimental data. (AJM1 4.33) This is Dr. Mattick's position even though he asserts a few pages later (when commenting on sufficiency of disclosure), that "computer programs were *readily available* in 1994 to generate" information about "all of the antigenic sites on the VEGF-2 molecule." (AJM1 4.83). His opinions on these antibody issues are inconsistent.

2.4 In stark contrast, the declarants that HGS asked to evaluate the quality of the teachings of the opposed application have taken a very lenient approach. These declarants appear to have accepted that VEGF2 can be expressed in the manner suggested in the opposed application,¹ even though there is not a single experimental example in the opposed application in which the inventors report successful expression of VEGF2 in a cell. (See OPR1 at 3.4.2, 3.5, 4.6.2.2, and 7.6) The HGS declarants have also accepted that VEGF2 has certain biological activities, even though the opposed application contains no evidence whatsoever of biological activity, and the declarants do not appear to have performed any biological activity testing of their own. (OPR1 at 2.3.2, 2.7.4, 3.4.2, 4.6, 4.6.1-4.6.5, 4.8, 5.4, 5.5, and 5.9) These declarants have also accepted that VEGF2 can be used to diagnose or treat a wide variety of diseases, even though the opposed application contains no evidence whatsoever that VEGF2 can be used for such purposes. (OPR1 at 2.3.3-2.3.4, 3.7.1, 4.6.3, and 6.8.1-6.8.4.)

2.5 In my opinion, these two extreme approaches are irreconcilable. The experiments performed by Dr. Alitalo and described in his first declaration are more relevant to the adequacy of the teachings in the opposed application than the experiments (or lack thereof) described in the application itself, or the experiments by Dr. Power (discussed below in greater detail), which are not based on the teachings in the opposed application. (And, had HGS raised any legitimate criticisms of Dr. Alitalo's first declaration, the criticisms have been fully addressed by the experiments Dr.

¹ See, e.g., AJM1 at 4.19-4.23 (Mattick cataloging uses for VEGF2 alleged in the opposed application) and 4.24 (Mattick concluding that these unsupported uses "constitutes the basic information that I would have required in 1994 to use VEGF-2 in a wide range of biological activities.") [See AJM1 at 3.31, 3.33, 4.3-4.13, 4.77-4.78; AJG1 at 6.5, 6.8, 6.11, 7.24, 7.46, 7.48; ANH1 at 3.15, 3.19-3.23, 3.26, 4.20; ATR1 at 9-12; ASA1 at 6 and 17]

Alitalo describes in his second declaration.)² When all of the scientific evidence in the opposition proceeding is viewed objectively, one finds direct evidence (from Dr. Alitalo, two sets of experiments) that the VEGF2 invention does not work as it was described in the opposed application, because it is incomplete. Neither the opposed application nor the HGS declaration present any evidence to suggest that VEGF2 as described in the patent application works. The choice of the HGS declarants to discount the scientific evidence and accept the teachings in the patent application about VEGF2 is not based on any scientific principles.

- 2.6 Dr. Gamble's declaration provides another excellent example. There is *direct experimental evidence* underlying Dr. Alitalo's declaration that VEGF2 taught in the application cannot be expressed and secreted. Yet notwithstanding that evidence, Dr. Gamble says, "In my opinion Dr. Alitalo's conclusions represent pure speculation and cannot reasonably be drawn from the results presented in his statutory declaration" Yet, Dr. Gamble apparently approves of the opposed application and its teachings, even though none of the teachings relating to VEGF2 or its expression or activity are based on reported experimental evidence. I note that when Dr. Gamble critically evaluates the scientific merit of a patent application, her standard is that "whether a patent specification gives examples of biological activity would seem to me to be largely irrelevant." (AJG1 7.18) In my opinion, her standards for scientific evaluation of declaration documents and patent documents are simply irreconcilable. There are other examples as well:

² Dr. Alitalo's first declaration demonstrated that VEGF2 cannot be expressed and secreted as taught in the opposed application. The HGS declarants argued that these results were not reliable because the experiments lacked appropriate controls, for example, but did not present any of their own experiments to show successful expression and secretion. As reported in his second declaration, Dr. Alitalo re-ran his experiments using the controls suggested by HGS and addressing other concerns raised by them, and showed again that VEGF2 cannot be expressed and secreted as taught in the opposed application. In my opinion, his second declaration further validates his first declaration and addresses the criticism raised by HGS. Dr. Alitalo's experiments are really the only evidence on this important subject in this opposition proceeding, because the opposed application contains no evidence of successful expression and secretion of VEGF2 by cells, and HGS provided no such evidence in any of its declarations. (Dr. Power says she expressed and secreted a protein, but the expression experiment that she described is not based on what HGS taught in its application.)

2.6.1 Dr. Gamble "would expect that VEGF2 could be expressed and secreted and would be biologically active (AJG1 at 6.5), even though the application contains no evidence that it can be expressed or secreted. She seems to expect that such expression would be routine in virtually any type of cell, even though the application failed to show expression in any cell types. (AJG1 6.6.) In my opinion, this assertion is simply pure speculation.

2.6.2 Dr. Gamble's opinion is that the mere identification of a DNA sequence and the inherent information it provides, combined with the teachings in the patent specification, "makes possible the manifest therapeutic benefits, which VEGF-2 has to offer, and which will be obtained in the future." (AJG1 at 6.6) She holds these opinions even though the application has no experimental evidence of VEGF2 biological activity, and certainly no evidence that VEGF2 is therapeutic for any disease. In my opinion, in light of the objective scientific evidence, her expressed opinion is pure speculation.

2.6.3 Dr. Gamble finds that the application provides "information concerning gene therapy to provide therapeutic and prophylactic effects against a wide range of different disease states". (AJG1 at 6.8.10) However, the application provides no evidence of gene therapy. Additionally, in all of medicine, there are not currently "a wide range of different disease states" that are treated with gene therapy (using any known gene). Again, in my opinion, in light of the objective scientific evidence, her expressed opinion is pure speculation.

2.6.4 Dr. Gamble finds that the application indicates that VEGF-2 could be isolated from a human cell library from a human embryo, from osteoclastomas, from adult heart, or from adult breast cancer cell lines (AJG1 6.8.3), even though the application fails to demonstrate isolation of VEGF2 protein from any source whatsoever. In my opinion, in light of the objective evidence, her expressed opinion is pure speculation.

2.7 While these are only a few of the examples I could give, I believe my point is clear. Applying a uniform and scientifically objective standard, it would make no sense to

disbelieve a carefully planned and executed experiment by Dr Alitalo, the scientist who is perhaps more familiar with VEGF-C and the VEGF2/VEGF-C gene than any other scientist, if journal publications are any indication, but instead to believe a patent application that speculates widely but has no underlying experimental support.

B. MIS-QUOTES AND CROPPED QUOTES

- 2.8 The HGS declarants frequently say that they are quoting from or paraphrasing statements from my first declaration, and then responding to them. Occasionally, the quotes are incomplete, or out of context, and fail to capture my full thoughts and opinions on subjects. Sometimes, the paraphrases are simply inaccurate. In some cases, HGS declarants say that are responding to my declaration, when they are not. It is important to read my declaration in context to determine whether the HGS declarants have really responded to what I have said, and not rely on their representations.

C. FAILURE TO ANALYZE FROM THE STANDPOINT OF SCIENTISTS HAVING COMMON GENERAL KNOWLEDGE IN THE FIELD.

- 2.9 It is my understanding of Australian patent law that most patentability issues are analyzed from the viewpoint of an individual possessed of the common general knowledge in the field of the invention, in Australia, at the time that the patent application was filed. However, this is not always the approach taken by at least some of HGS's declarants.
- 2.10 For example, Dr. Mattick explicitly states that his instructions from HGS were "To review the patent specification and to describe what it would have conveyed to me had I read it in March 1994." (AJM1 at 2.3.1 (emphasis added).) Dr. Mattick was also instructed "To base all comments presented herein on my knowledge as at 8 March 1994, unless I specifically state otherwise." (AJM1 at 2.3.3 (emphasis added).) A vast part of Dr. Mattick's declaration explicitly sets forth this personal point of view, i.e., conclusions that Dr. Mattick personally believes that he would

have drawn or results that he believes he could have personally achieved. (AJM1 at, e.g., 3.33, 4.13, 4.73, and 4.77.) To the extent Dr. Mattick's (or other declarants') prominence and experience and positions gave him knowledge greater than the common general knowledge in Australia in 1994, many of the personal opinions expressed in his declaration may not be relevant to patentability issues.

D. FAILURE TO CONSIDER ALL RELEVANT EVIDENCE

- 2.11 It is not clear from the evidence submitted whether all of HGS's experts considered all of the relevant evidence in reaching their opinions expressed in their declarations.
- 2.12 For example, Ludwig Institute's evidence in opposition included a declaration from Professor Alitalo setting forth evidence that VEGF2 as taught in the HGS application is incomplete and is not expressed and secreted as a growth factor by cells. In my opinion an expert providing an opinion as to the sufficiency and fair basis of the HGS application should have considered evidence about whether the invention works as HGS alleged that it would. It is not clear that Dr. Mattick, Dr. Power, or Dr. Rapoport gave due consideration to the Alitalo declaration.

E. IS VEGF2 THE SAME AS VEGF-C?

- 2.13 Dr. Mattick explains that "HGS' Patent Attorneys have informed me that VEGF-2 and VEGF-C are the same molecule." (AJM1 at 3.3.) Dr. Gamble says "Today, VEGF-2 is identified by the nomenclature VEGF-C. When I read VEGF-2 in the patent specification I understand it to mean VEGF-C" (AJG1 at 3.1.) Dr. Rapoport says, "It is my understanding that VEGF-2 and VEGF-C are terms used to refer to the same molecule." (ATR1 at 13.) Dr. Rapoport uses the two terms interchangeably. (ATR1 at 13.) This position requires clarification.
- 2.14 As I stated in my earlier declaration, it is probably true that VEGF2 and VEGF-C were *derived from* the same human gene. (See OPR1 at 1.5.1.) However, these are

names given by two different research groups to the results of their own research, which differed substantially. The advice from HGS's attorneys or the assumption that these terms can be used interchangeably glosses over substantial differences between the secreted growth factor "VEGF-C" described in patent and scientific literature by Alitalo et al.,³ and the incomplete "VEGF2" sequence taught in the opposed application, that is apparently never secreted⁴ and has never been reported in the scientific literature to have significant biological activity. (I repeat by reference my discussion of the inadequacy of the description of VEGF2 in OPR1 at, e.g., 1.5.1-1.5.2, 4.4-4.7 and 4.11-4.11.2.) To the extent that Dr. Mattick or Dr. Gamble or Dr. Rapoport believed that any of the scientific literature that has been published relating to VEGF-C is relevant to patentability issues for the *incomplete VEGF2* taught in the opposed application, they have based their declarations on incorrect assumptions. The experiments described in Professor Alitalo's two declarations (hereinafter OKA1 and OKA2) demonstrate that the incomplete VEGF2 taught in the opposed application cannot be expressed and secreted.

- 2.15 Dr. Hayward clearly intermingles his knowledge of VEGF-C with the teachings in the opposed application relating to VEGF2. For example, Dr. Hayward declared, "I am aware that VEGF-2 is proteolytically processed upon secretion from cells in vivo to form the naturally occurring ligand for the Flt-4 and the KDR/Flk-1 receptors. I would expect a fusion of the 350 amino acid sequence of VEGF-2 to a signal sequence to be proteolytically processed to produce functional VEGF-2." In reality, scientists such as the group led by Alitalo et al. have demonstrated that a heavily processed form of VEGF-C (lacking about 102 amino acids from the beginning (N-terminus) and about 190 amino acids from the end (C-terminus)) binds and stimulates the Flt4 and KDR/Flk-1 receptors. (See, e.g., Documents D70-D74.) The opposed application does not teach that VEGF2 is a ligand for any receptor, and does not teach

³ See, e.g., OPR1 at 1.5.3-1.5.4 and Documents D71-D74.

⁴ See Alitalo Declaration filed by Ludwig Institute as part of evidence in opposition.

that VEGF2 is processed in a manner similar to VEGF-C, and does not teach to fuse the 350 amino acids of VEGF2 with an extra foreign signal sequence. Instead, the application teaches that full length VEGF2 is 350 amino acids which includes a signal sequence of about 24 amino acids and mature VEGF2 of about 326 amino acids. By contrast, Dr. Alitalo's declarations establish that VEGF2 as taught in the opposed application is not expressed and secreted at all. When HGS determined that VEGF2 in the opposed application was incomplete, and filed a second patent application (Document D43) on the 419 amino acid VEGF2 more than a year later, HGS still failed to teach that VEGF2 was a ligand for Flt4 or any other receptor, and failed to teach the VEGF-C processing that was elucidated by Professor Alitalo's group. Thus, Dr. Hayward's "awareness" of VEGF2 processing relates to Dr. Alitalo's VEGF-C, and not HGS's VEGF2.

- 2.16 Dr. Rapoport devotes a significant part of his declaration to discussing biologically active VEGF-C molecules invented by Alitalo and Joukov. (See, e.g., ATR1 at 13-15.) It is important to remember that Alitalo and Joukov taught VEGF-C "biological activity" (e.g., binding to Flt4 receptor and stimulation of lymphatic endothelia) that were not suggested by (and owe nothing to) the opposed application. The suggestion that the Alitalo work confirms teachings in the opposed application is entirely misleading. (See, e.g., ATR1 at 16.)

LACK OF NOVELTY AND INVENTIVE STEP OF CLAIMS OF THE OPPOSED APPLICATION

- 3.0 In Section 2 of the OPR1 declaration, I explained that at least claims 1-4, 13-28, and 34-61 in the opposed application were broad enough to encompass materials and methods that had been taught in the prior art literature that predated HGS's earliest alleged priority date of 08 March 1994. The prior art upon which I drew these conclusions did not teach the exact VEGF2 DNA or deduced amino acid sequences in the figures or sequence listing of the opposed application, but the claims at issue are not limited to exact, full length VEGF2 sequences.

- 3.1 In this section I explain that the HGS declarants consistently fail to identify any explicit claim language that excludes the prior art that I identified in my first declaration. I address the particulars of the HGS declarations below, but I maintain my original opinion, expressed in OPR1, that most or all of the claims encompass the prior works of others.
- 3.2 The HGS declarants' principal response to the references cited in my first declaration that demonstrate that the application lacked novelty comprises generalized statements that a practitioner in the appropriate field of research would be able to distinguish VEGF2 fragments, analogs, derivatives, variants, and other genera of molecules claimed in the opposed application from prior art polynucleotides and polypeptides (e.g., VEGF, PDGFa, PDGFb, PlGF, and fragments, analogs, and derivatives thereof disclosed or suggested in the prior art.). A consistent shortcoming of these declarations is the *failure to point to any language in the claims* that defines VEGF2 molecules in a way that excludes prior art molecules.
- A. "Fragment, Analogue, or Derivative" Language Fails to Exclude the Prior Art from the Claims.
- 3.3 Several claims in the opposed application are not limited to the exact VEGF2 sequences because they are directed to a "fragment, analogue or derivative" of a VEGF2 polypeptide (e.g., claim 28) or to a polynucleotide encoding a "fragment, analogue or derivative" of a VEGF2 polypeptide (e.g., claims 1-4, 21). According to the specification, fragments, derivatives, or analogues may be VEGF2 polypeptides modified such that one or more of the amino acid residues of VEGF2 are substituted with conserved or non-conserved amino acid residues, and/or ones in which additional amino acids are fused to the mature polypeptide. (See, e.g., opposed application at pp. 9-10.) Also, polypeptides resulting from deletion of amino acids would still fall within the commonly accepted definition of "fragment, analogue, or derivative." (See also opposed application at page 7, discussing "deletion variants, substitution variants, and addition or insertion variants.")

3.4 In OPR1 I explained that the prior art taught DNA sequences and polypeptides, such as VEGF, PlGF, PDGF-a, and PDGF-b, that differed from the exact VEGF2 DNA and amino acid sequences taught in the opposed application, but still fell within the opposed application's definition of "fragment, analog, or derivative." (See OPR1 at 2.2-2.2.2, 2.3, 2.7.1, 2.7.9, and 2.7.20.) Much of the opponent's evidence in answer is directed to a philosophical discussion of whether these prior art polypeptides, which although they satisfy the literal definition of VEGF2 "fragment, analogue, or derivative", should nonetheless be considered to fall outside the scope of the claims.

3.5 The opposed application says that "it is particularly important that all eight cysteines are conserved within all four members of the family...." These eight cysteines are the only VEGF2 amino acids that the opposed application seems to say should remain unchanged when designing fragments, analogs, or derivatives. However, the application itself admits that the eight cysteines are a feature that VEGF2 already has in common with prior art family members VEGF, PDGFa, and PDGFb. Thus, the opposed application places no restrictions when designing fragments, analogues, and derivatives that would prevent one from arriving at these prior art polypeptides. In other words, all of these prior art molecules (which already contained the eight cysteines) could fairly be classified as VEGF2 fragments, analogues, or derivatives as those terms are used in the opposed application. (See, e.g., OPR1 at 2.2 - 2.2.2.) The claims do not restrict the number of modifications to the VEGF2 sequence that a VEGF2 fragment, analogue, or derivative can contain, so in effect, VEGF2 could be modified until it matched VEGF, PlGF, or PDGF.

3.6 None of the HGS declarants actually contest my analysis that the *claims* fail to recite restrictions on "fragment, analogue, or derivative" that would serve to exclude the prior art polynucleotides and polypeptides such as VEGF, PDGFa, PDGFb, and PlGF. In fact, Dr. Mattick basically admits that *the claims* set forth no maximum number of changes that can be made to a protein that is to be classified as a VEGF2 fragment, analog, or derivative; he simply would not require that as part of the patent laws. (See AJM1 4.37.)

3.7 Instead of finding *claim limitations* that exclude the prior art, the HGS declarants have proposed a subjective “looks more like” standard for *interpreting* the claims that they say would exclude VEGF and the PDGFs from the claims:

3.7.1 For example, Dr. Mattick said: “I would not require the patent specification to set a maximum limit of modifications that can be made to a protein before I could reasonably ascertain whether a protein was a fragment, analogue, and/or derivative of VEGF-2. . . . As soon as a protein starts to look more like VEGF, PDGFa, PDGFb, or PlGF, it would not, in my opinion, be a fragment, analogue and/or derivative of VEGF-2. Thus, I would not regard any of VEGF, PlGF, PDGFa or PDGFb to be VEGF-2 fragments, analogues and/or derivatives.” (AJM1 4.37; see also AJM1 4.26.)

3.7.2 Similarly, Dr. Gamble said: “For something to be a fragment, derivative or analogue of a molecule it must not only share a biological function or activity with VEGF-2 but it must also have homology at the primary amino acid level. Thus, a peptide or polypeptide that more closely resembles VEGF, PDGFa, PDGFb or PlGF, than VEGF-2 at the primary amino acid level would not be a VEGF-2 fragment, derivative or analogue. Such an interpretation is inherent in the meaning of these terms and is consistent with the general manner in which others and I use these terms in everyday scientific language.” (AJG1 at 7.12. See also AJG1 7.25 - 7.27)

3.7.3 Similarly, Dr. Hayward declared that there is not sufficient sequence identity between VEGF2 and PDGF, VEGF, or PlGF for these molecules to be considered derivatives of VEGF2. (See, e.g., ANH1 at 3:8, 4.2.) Dr. Hayward fails to explain what minimum sequence identity is required, and, of course, the claims do not set a minimum sequence identity.

3.8 This "looks more like" approach is unworkable. It is highly subjective, vague, has no basis in the opposed application, and would cause the scope of the claims to change over time.

3.9 First, the approach that HGS is advocating is contrary to the understanding of patent law given to me by Ludwig Institute's attorneys. It is my understanding that the words of the claim are supposed to define its scope, not subjective "looks like" criteria. The reader is supposed to be able to determine whether or not something falls within a claim by criteria that are reasonably clear.

3.10 In fact, the application discloses no clear standards for deciding whether a theoretical analog "looks more like" VEGF or VEGF2, and there are no universal standards in the field of the invention, either. In the context of proteins, the "looks like" criteria could be based on percent amino acid similarity, or on three-dimensional shape, or on size, or more subtle criteria, such as whether amino acids that are believed to be essential for activity are more like those found in VEGF or VEGF2.

3.10.1 To give one hypothetical example, the VEGF2 polypeptide has an approximately 190 amino acid stretch that shares homology with a silk protein. (See OPR1 at 4.11.1.3 and Document D71, Joukov et al., EMBO J 16:3898-3911(1997)) Removal of most or all of this large portion of VEGF2 would give the resultant VEGF2 fragment a size much more similar to the size of VEGF. Further, the folded shape of the truncated VEGF2, missing this silk-like domain, might be expected to look much more like the three-dimensional shape of VEGF polypeptides having a similar size. But this fragment has 100% amino acid identity with a portion of VEGF2 and much lower amino acid identity with VEGF. Under Dr. Mattick's "looks like" criteria, its not clear whether or not we have a molecule within HGS's claims, because it is unclear whether size, or shape, or % identity, or other properties are the most important criteria.

3.10.2 To give another example, mature VEGF-C has an amino acid sequence nearly identical to a portion of VEGF2, if the approximately 190 BR3P-like amino acids are removed from the C-terminus, and still more amino acids are removed from the N-terminus of VEGF2. This molecule will bind one of the two VEGF receptors (VEGFR-2), whereas VEGF2 will not. (See OPR1 at 4.11.1.3 and Joukov et al., EMBO J 16:3898-3911(1997)) It is unclear under the “looks like” criteria whether one should classify VEGF-C as a VEGF2 analog (because of amino acid sequence identity) or a VEGF analog (because of receptor binding properties). Receptor binding properties would be one of the most important practical criteria for scientists who wished to develop therapeutic applications for a putative growth factor, which clearly seems to be a goal of the opposed application. (It is generally through cellular receptors that growth factors exert their effects in the body.)

3.11 The opposed application itself says nothing whatsoever about the “looks more like” standard for delimiting the boundaries of “fragment, analogue, or derivative.” In fact, the opposed application fails to mention any standard.

3.12 Another troubling aspect of HGS’s approach is that the scope of the claims will change with time, as new genes are discovered, because the scope of “fragment, analog, or derivative” would continue to change as more genes are discovered. This problem is best illustrated with two real-world examples.

3.12.1 If we placed ourselves back in time to March, 1994, and were given the sequence of VEGF2 and asked to characterize it, the proper answer, according to the “looks more like” standard, would have been to call it a “VEGF fragment, analog, or derivative.” The reason for this conclusion *at that time* would have been that the VEGF2 sequence more closely resembled VEGF (30% amino acid identity) than any other known protein at the primary amino acid level. (See Figure 3 of the opposed application.) VEGF2 “looked more like” VEGF than other known molecules. Using the logic of Dr. Mattick and

Dr. Gamble, the VEGF2 sequence would have been a mere analogue or derivative of VEGF.

3.12.2 Some time after 1994, the VEGF-D gene and protein were discovered by Achen et al. (See OPR1 at 4.12.1; and Document D67.) VEGF-D has greater amino acid percent identity to VEGF2 than it has to VEGF. Under the HGS "looks more like" criteria, VEGF-D might be considered to fall within the HGS claims (because it is more similar to VEGF2 than VEGF). On the other hand, VEGF-D is a separate human protein in its own right, encoded by its own gene, that owes nothing to the discovery of VEGF2. (See OPR1 at 4.12.1.) It would make no more sense to call VEGF-D an analog or derivative of VEGF2 than it would have made to call VEGF2 a mere analog or derivative of VEGF, when VEGF2 was discovered (due to shared amino acid motifs and allegedly shared biological activities).

3.12.3 The logical extension of saying that a newly discovered protein (such as VEGF-D) is *not* a fragment, analog, or derivative of a previously discovered one (such as VEGF2) is that the scope of HGS's patent claims to VEGF2 fragments, analogs, and derivatives becomes narrower each time a new gene family member, such as VEGF-D, is discovered. In other words, before the discovery of VEGF2, all of the analogs that looked more like VEGF than PDGF would have been called VEGF analogs. Then, when VEGF2 was discovered, some of those "VEGF analogs" would have needed to be reclassified as "VEGF2 analogs" because they looked more like VEGF2 than VEGF. In fact, all of the VEGF analogs that looked more like VEGF2 than VEGF or the PDGFs would have been reclassified as VEGF2 analogs. But then, when VEGF-D was discovered, some of those analogs would more properly be classified as VEGF-D analogs, because they were more similar to newly discovered VEGF-D than to VEGF, VEGF2, or the PDGFs.

3.12.4 My purpose with this exercise is to show that if you try to apply a "looks more like" standard for interpreting the claims directed to fragments, analogues, and

derivatives, then the breadth of the claim gets narrower every time someone discovers a new member of the VEGF family. The idea that the scope of patent claims changes each time a new VEGF family member is discovered is contrary to my understanding of the clarity requirement of the patent laws. It would cause confusion and uncertainty for scientists trying to interpret the claims.

3.12.5 To summarize, the literal scope of “fragment, analogue, or derivative” claims embraces VEGF, PDGFa, and PDGFb, all of which were known in the field and described in the literature before the priority date of the opposed application. The subjective “looks more like” standard proposed by HGS to avoid this confusion has no support in the application or the claims. It is unworkably vague and causes the scope of the claims to change over time.

B. VEGF2 “Activity” Language Fails to Exclude the Prior Art from the Claims.

3.13 A number of the claims of the opposed application use an activity limitation to attempt to define which polynucleotides and polypeptides fall within a claim and which ones do not. I explained in my first declaration that the list of activities ascribed to VEGF2 by the opposed application are merely activities that have been ascribed to VEGF, PDGF, and/or PlGF prior art polypeptides. (See, e.g., OPR1 at 2.3-2.3.5.) For this reason, claim limitations directed to “VEGF2 activity” fail to exclude the aforementioned prior art polypeptides, because the only teachings in the opposed application relating to VEGF2 activity are predictions that VEGF2 will share activities that other scientists had identified in the aforementioned prior art polypeptides. (See OPR1 at 2.3-2.3.5, 2.7.4, 2.7.9, and 4.6-4.8.)

3.14 None of HGS’s declarants contest the fact that claims which recite “VEGF2 activity” fail to recite an activity that is unique to VEGF2 and that would serve to exclude prior art polypeptides such as VEGF, PDGFa, PDGFb, and PlGF.

3.15 Dr. Gamble and others ask the Patent Office to accept that VEGF-2 biological activity means "angiogenic activity" and optionally others. (See, e.g., AJG1 7.9-7.11; 7.15-7.18; and 5.14-5.22. See ANH1 at 3.6) There are several problems with their analysis, including the following:

3.15.1 First, even if we accept her selected definition, angiogenic activity fails to exclude prior art vascular endothelial growth factor (VEGF) polypeptides from the claims, because VEGF polypeptides are angiogenic, as admitted in the opposed application (background) and in Dr. Gamble's own papers. (See, e.g., Cockerill, Gamble, and Vadas, Annexure GBC-9 in the HGS evidence in reply, at page 136.) In fact, if angiogenic activity is sufficient for VEGF2 activity, then according to Dr. Gamble's publications, PDGF polypeptides are embraced as well. (See Litwin, Gamble, and Vadas, Annexure GBC-10 of the HGS evidence, at page 105 (PDGF "has roles in wound healing and angiogenesis").)

3.15.2 Second, the claims are not restricted to angiogenic activity, and the application teaches that VEGF2 has numerous activities other than angiogenic activities. (See OPR1 at 2.3.3-2.3.5.)

3.15.3 Third, there is simply no evidence that VEGF2 as taught in the patent application has angiogenic activity (or any of the other activities alleged).

3.16 As a related matter, Dr. Gamble declared that an endothelial growth assay could distinguish VEGF2 polypeptides, fragments, analogues, and variants from PDGF polypeptides, analogues, and variants:

"As an additional point of distinction between VEGF-2 and PDGFa, or PDGFb is that PDGFa and PDGFb do not promote the growth of endothelial cells. Thus had I wanted to distinguish a VEGF-2 fragment, analogue or derivative from any one of these proteins, I could have easily performed one or more assays, such as those identified in paragraph 5.15, above. Such assays could be performed to show that the analogue, fragment or derivative

contained an endothelial cell proliferative activity, while the comparator molecule (such as PDGFa and PDGFb) did not contain such an activity. Such a result would clearly have distinguished a VEGF-2 analogue, fragment or derivative from PDGFa, or PDGFb.” (AJG1 at 7.11)

3.17 Dr Gamble’s proposition is not correct. First, it is important to re-emphasize that the opposed application teaches that VEGF2 shares biological activities of PDGFa and PDGFb. (See OPR1 at 2.3.3-2.3.5.) Since VEGF2 supposedly has activities other than endothelial growth activities, including PDGF-like activities, it is not clear to me whether the results of only an endothelial cell growth assay would reliably exclude PDGF proteins from the definition of proteins with VEGF2 activity. (See discussion below relating to lack of clarity.) Second, prior art VEGF polypeptides have endothelial cell growth activity, so even if “VEGF2 activity” meant a combination of angiogenic and endothelial cell growth activities, the claims would still encompass prior art VEGF subject matter.

3.18 Dr. Hayward’s position regarding “VEGF2 activity” is that he does not understand why a unique defining activity that discriminates VEGF2 from prior art polypeptides (PDGF, VEGF) is necessary at all. He feels that once a substantial portion of the primary amino acid sequence is available, the sequence provides the essential defining characteristic. The answer to Dr. Hayward is that many of the claims (e.g., those that recite fragment, analogue, or derivative and those that recite antibody binding) do not explicitly require the presence of a substantial portion of the primary VEGF2 amino acid sequence. Those claims have neither structural nor functional (activity) limitations that exclude the prior art. If a claim fails to exclude the prior art with structural or functional or other limitations, then the claim encompasses the prior art.

C. “Hybridization” Claim Language Fails to Exclude the Prior Art from the Claims.

3.19 A number of the claims in the opposed application use a hybridization limitation to attempt to define which polynucleotides and polypeptides fall within a claim and which do not. I explained in my first declaration the nature of hybridization experiments, and also that whether two polynucleotides hybridize to each other is dependent on both the relationship of the molecules (complementarity) *and* the conditions under which the hybridization experiment is conducted. (See, e.g., OPR1 at 2.4-2.4.3.) Hybridization experiments are binding experiments with which scientists can determine the relatedness of polynucleotides, and I previously explained that scientists can adjust the experimental conditions (e.g., temperature, ionic strength of solutions used) to increase or decrease the stringency of the experiment and thereby increase or decrease the group of hybridizing polynucleotides. I explained that the HGS claims require no minimum level of stringency that would serve to exclude prior art DNAs/proteins from the claims. (See OPR1 at 2.4-2.4.3, 2.7.5, and 2.7.11-2.7.12.)

3.20 None of HGS's declarants contest the fact that *claims* which recite "hybridization" language fail to *recite hybridization conditions* that would serve to exclude prior art polynucleotides or polypeptides such as VEGF, PDGFa, PDGFb, and PlGF.

3.20.1 Dr. Mattick says that when he reads the hybridization language of the claims *in combination with the description of hybridization set forth in the patent specification*, he would understand "it" to mean that hybridization conditions should be sufficiently specific to exclude known, non-VEGF-2 sequences. He says it would have been routine to perform hybridizations to avoid cross-reactivity with prior art sequences. (AJM1 4.28-4.30, 4.39, and 4.49-52.). Thus, Dr. Mattick does not dispute that the *claims* contain no hybridization stringency limitations whatsoever. Dr. Mattick believes the hybridization claims avoid the prior art because exemplary conditions *in the application* should be interpreted as restrictions on the hybridization claims, even though the claims do not contain the hybridization conditions.

3.20.2 Dr. Hayward discusses hybridization at ANH1 3.9 - 3.12 and 4.11-4.15. He admits that varying the hybridization conditions will affect the number of

inexact polynucleotide matches that will hybridize to a target sequence (ANH1 at 3.10), and, like Dr. Mattick, finds an example of conditions *in the specification* which he says will prevent cross-hybridization (ANH1 at 3.11). He says that cross-hybridization would be unlikely *under suitable conditions such as those provided in Example 1*. (ANH1 at 4.11.) However, he does not dispute that such hybridization conditions are not explicitly recited in the claims themselves.

3.21 In view of the comments by the HGS declarants, I have reviewed the application again to determine if the application says that, whenever claims recite hybridization language, the hybridization should be understood to occur under particular conditions. I find no instruction of this nature whatsoever.

3.22 My review of other HGS documents further convinces me that the hybridization claims do not exclude the prior art. It appears from other published patent applications that, when HGS intends to limit its claims to certain hybridization conditions, or limit claimed fragments, analogs, or derivatives to those with minimum levels of sequence identity, HGS includes such limitations in the claims.

3.23 Filed with this declaration are Exhibits PAWR-1 to PAWR-3, which I understand represent the claims of published patent documents from Human Genome Sciences relating to other DNA and protein inventions. When I examine the claims of those applications, I see explicit limitations like the following:

3.23.1 Exhibit PAWR-1 comprises claims from Human Genome Sciences Australian Patent Publication No. 714484, also directed to Vascular Endothelial Growth Factor 2, and having common inventors with the opposed application. I observe the following claiming conventions employed by HGS with respect to that VEGF2 invention, which were not employed with respect to the VEGF2 invention in the opposed application:

Claim 1, part m: When claiming polynucleotides that hybridize to a reference polynucleotide, HGS specified polynucleotide fragments

which hybridize "under the following conditions: hybridisation in 0.5 M sodium peroxide NaPO₄, 7% sodium dodecyl sulfate (SDS) at 65°C and washing with 0.5 x SSC, 0.1% SDS at 60°C or equivalent hybridisation stringency." (See also claim 14, 16(m), and 29.)

As I explain in my first declaration, factors such as temperature and solutions used in a hybridization experiment establish (limit) which molecules will "hybridize" and which will not. (See OPR1 at 2.4-2.4.3.) Exhibit PAWR-2 which comprises claims from HGS Australian Patent Publication No. 726486, includes claims reciting similar hybridization conditions. (See, e.g., claims 33-34.)

3.23.2 Exhibit PAWR-3 comprises claims from Human Genome Sciences

Australian Patent Publication No. 708972. I observe the following claiming conventions employed by HGS with respect to that invention, which were not employed with respect to the VEGF2 invention of the opposed application:

When claiming homologues or analogues of a reference sequence, the claims include a "percent identical" limitation which restricts the amount of variation permitted from the original sequence. See, e.g., claim 1, part (h), or claim 6: claim 1 part (n) ("capable of hybridizing . . . and which is at least 70% identical"). Also when claiming variants, claims include a "conservative" limitation which restricts the types of variations that are introduced. See, e.g., claim 15 part (l) ("variant . . . wherein said variant results from conservative substitutions.")

Percent identity language and conservative substitution language serve to limit the amount of variation that is permitted in the molecule.

3.23.3 I have not reviewed these other patents for their merit and express no opinion about the appropriateness of the scope of their claims. Nor do I express an opinion at this time about whether the foregoing types of limitations would cure defects in the claims of the opposed application. I make reference to these documents only to contrast the claim language that HGS used in them to the claim language used in the opposed application. Dr. Mattick would read

the claims of the opposed application to incorporate hybridization or other limitations found in the text of the application. Dr. Mattick's analysis fails to explain why HGS sometimes chooses to include hybridization limitations, percent identity limitations, and other limitations in patent claims and other times does not, if HGS always intends to have its claims limited by such conditions.

D. Limitations in the Claims Relating to Antibody Binding and Antibodies Fail to Exclude the Prior Art.

3.24 Claims 16-20 and 40-45 of the opposed application recite a genus of any polypeptides that would be bound by any antibody that binds VEGF2. I explained in my first declaration that these claims encompass prior art polypeptides. (See, e.g., OPR1 at 2.5 and 2.74-2.75.) I explained that at least some antibodies that were capable of binding to VEGF2 would be capable of binding to prior art polypeptides, and that consequently, antibody binding limitations of claims failed to exclude the prior art. (See OPR1 at 2.5, 2.7.12, and 2.7.15.)

3.25 Dr. Mattick and Dr. Gamble believe that one cannot conclude that these claims are anticipated, in the absence of actual tests showing cross-reactivity, and that the claims cannot be analyzed on a theoretical level. (See, e.g., AJM1 4.31-4.34, 4.40, and 4.48; AJG1 at 7.21.)⁵ There are several flaws in Dr. Mattick and Dr. Gamble's analysis.

3.26 First, Dr. Mattick contradicts himself only a few pages later, when he declares that "computer programs were readily available in 1994 to generate" information to identify "all of the antigenic sites on the VEGF-2 molecule." (See AJM1 4.83.) It

⁵ In paragraph 4.48 Dr. Mattick speaks of whether the amino acid sequence "preferentially binds" a VEGF2 antibody. I'm not sure what "preferential" binding means, and whatever it means, it is not a requirement of the claims. Only "binding" is required by the claims.

makes no sense to urge that antibody binding defies theoretical analysis if computer programs were readily available seven years ago that could identify all antigenic sites on a protein.

3.27 Second, the scientific literature contradicts the conclusions drawn by Drs. Mattick and Gamble. For example, Harlow et al., *Antibodies, a Laboratory Manual*, Cold Spring Harbor Laboratory Press (1988) (cited in the Statement of Grounds and Particulars as a treatise that formed part of the common general knowledge in 1994, and also in OPR1), instructs that synthetic peptides as small as six residues in length "will consistently elicit antibodies that bind to the original protein." (See Harlow at page 76 which is Exhibit PAWR-4 to this declaration). I explained in my original declaration (OPR1 at 2.74-2.75) and Dr. Gamble has confirmed (AJG1 at 7.13) that the VEGF2 sequence and prior art sequences share at least one or two stretches of 6 or 7 amino acid (100%) identity. According to conventional wisdom, these peptides can be expected to elicit antibodies that bind to "the original protein," from which the peptides were derived. In other words, conventional wisdom in the field is that these peptides can be expected to elicit antibodies which would bind both VEGF2 and also bind to the prior art protein (VEGF or PDGF) that shares the common peptide sequence. The personal opinions expressed by Drs. Mattick and Gamble appear to defy conventional wisdom on this subject.

3.28 Third, Dr. Mattick's opinion that one cannot meaningfully analyze the claim language relating to polypeptides that would bind an antibody that binds VEGF2 on a theoretical level *compels a conclusion that claims 16-20 and 40-45 of the opposed application are indefinite*. When one examines the HGS application, one sees that the inventors *failed to describe any actual antibodies to VEGF2*, yet the claims seem to encompass the theoretical universe of all antibodies that bind VEGF2. The opposed application does not even set forth the proper antibody binding assay to use to determine whether or not a protein is bound by an antibody that binds VEGF2. Thus, like it or not, the claims at issue *require* a theoretical analysis, if they can be given any meaning at all. If a common sense analysis of antibody science cannot be applied to analyze patent claim language, then patent examiners would be required to perform

absurd amounts of laboratory work or otherwise allow any patent claim relating to antibody binding. The public could never know with any certainty whether it was working with an infringing polypeptide because the public could never test it for binding against all VEGF2 antibodies. (See also discussion in paragraphs 5.4-5.4.4, below.)

3.29 Dr. Mattick's and Dr. Gamble's refusals to draw any conclusions about cross-reactivity and antibodies is another example of the double standard that they have applied to this proceeding. Scientists have decades of experience making and using antibodies, and the experience permits scientists to make predictions about cross-reactivity. For example, scientists would predict that if a first polypeptide has an epitope of about six amino acids, then an antibody to that epitope would probably bind the same six amino acid epitope of a second polypeptide. (See OPR 2.5.) There is a clear incongruity if Dr. Mattick refuses to draw conclusions about antibody binding on a theoretical level, but is willing to believe totally unsupported statements in the opposed application that VEGF2 fragments can be used to treat cancer and all of the other diseases and conditions listed in the opposed application. (See AJM1 4.19-4.24.) Predictions of antibody cross-reactivity due to common epitopes is at least as reliable as predictions of biological activity based on only 22-30% sequence identity, which the HGS application makes and the HGS declarants appear to accept on faith.

3.30 In my analysis of the prior art and novelty issues in my first declaration, I explained that scientists would not normally consider the immunogenicity of a protein to constitute a "biological activity" of the protein. (See OPR1 2.7.4) HGS challenges this position in its evidence in answer. (See, e.g., AJM1 4.45-4.46; ANH1 at 4.13)

3.31 At the outset, I would like to make clear that if immunogenicity constitutes a VEGF2 biological activity, then this only creates an additional reason why claims in the opposed application with "activity" limitations are not novel, as I explain in my first declaration. (OPR1 at 2.7.4.) The VEGF2 polypeptides will be expected to generate some of the same antibodies that are generated by prior art polypeptides.

3.32 HGS has called my explanation (that immunogenicity is not a "biological activity" of a putative growth factor) "spurious." (AJM1 at 4.45-4.46) The plain fact is that when scientists and doctors wish to develop a protein-based therapy, immunogenicity is an undesirable side-effect, and not a "biological activity". By way of illustration, I shall suppose that the biological activity of VEGF2 in the human body is to heal wounds. If one wants to administer VEGF2 as a pharmaceutical to treat wounds, then it is absolutely essential that the VEGF2 NOT be immunogenic. The consequences of VEGF2 being immunogenic (causing the body to make antibodies to VEGF2) could be catastrophic. For example, the antibodies that the body creates would be expected to neutralize the VEGF2 pharmaceutical that was administered. In addition, and more seriously, the body would continue to make VEGF2 antibodies which would neutralize the body's own VEGF2, making it harder or impossible for the body to naturally heal future wounds. In effect, patients being treated with VEGF2 to heal a wound would, as a side-effect, develop a potentially permanent and catastrophic autoimmune disorder. My illustration shows why an immune response to growth factor therapy would be considered highly undesirable. This illustrates by example why persons skilled in the art do not classify immunogenicity of a polypeptide (the ability to raise antibodies to it) together with those functions (e.g., growth factor functions) that are conventionally referred to as biological activities.

3.33 By way of additional illustration, I refer to Exhibit PAWR-5 (Skolnick and Fetrow, "From genes to protein structure to function: novel applications of computational approaches in the genomic era," *TIBTECH*, 18:34 (2000)), a relatively recent review article in the field of genomics that explores such issues as predicting what a protein does based on a protein sequence deduced from a DNA sequence. On page 34, the authors address the question, "What do we mean by protein function, the focus of this article?" The authors suggest function can have many levels and meanings, e.g., depending on whether one is looking at the protein function at a molecular level, physiological or metabolic level, cellular or phenotypic level, or the like. However, the ability to make antibodies to polypeptides is not among them.

E. Reply to Miscellaneous Specific Comments of the Evidence-in Answer

3.34 I offer the following additional comments to particular declarations in the HGS evidence in answer that appear to relate to the issues of novelty and inventive step.

a. AJM1 4.40

3.35 Dr. Mattick declared as follows:

"In paragraph 2.7 Associate Professor Rogers refers to a number of publications, which he says teach the subject matter claimed in the patent specification. I have reviewed each of documents D1, D5, D7, D12, D16, D18, D19, D20, D29, D34, D35, D36, D39 and D41. None of these documents describe VEGF-2." (AJM1 4.40)

3.36 This statement is not relevant to whether the claimed invention is novel. In my first declaration, I explained in detail that *the claims are not limited to VEGF2 molecules*, and that the aforementioned documents describe molecules that fall within the scope of the very broad claims. (See OPR1 at 2.7.)

3.37 Dr. Mattick further declared as follows:

"Further, to the extent that one or more of the claims in the patent specification might include a polypeptide that binds an antibody that binds to VEGF-2 I note that none of these publications describe an antibody that binds to VEGF-2 or establishes cross-reactivity between VEGF-2 antibodies and VEGF antibodies. These documents refer to such subject matter as VEGF, PDGF and PIGF." (AJM1 4.40)

3.38 This statement also is not relevant to the novelty of the polypeptide claims. To the extent that these publications disclose *a polypeptide* that binds an antibody that binds VEGF2, these publications destroy the novelty of the claims which recite this language. The fact that these publications use other names (VEGF, PDGF, PIGF) has no bearing on whether VEGF2 antibodies bind the polypeptides disclosed therein.

b. AJM1 4.43

3.39 Dr. Mattick declared as follows:

"The patent specification clearly identifies an isolated mRNA encoding VEGF-2. For example, Example 1 and Figures 4 and 5 of the patent specification teaches the isolation and detection of an mRNA species (see also the patent specification at page 27, lines 4 to 32). Furthermore, the isolation of VEGF-2 genomic DNA would have been a routine and straightforward task in 1994 for any person of ordinary skill in the field of molecular biology given the information in the patent specification." (AJM1 4.43)

3.40 I establish in my first declaration that the RNA allegedly identified in Example 1 does not appear to be a real mRNA from the gene that encodes VEGF2. (See OPR1 at 4.13.1 and 5.8.10.) Moreover, whatever RNA was observed in Example 1 was observed in a mixture of RNAs that were electrophoresed on a gel. The example does not describe an isolation. With respect to the genomic DNA, I observe that the genomic DNA that encodes VEGF2 encodes a protein of 419 codons, but the patent application only taught about 350 codons. When HGS discovered the missing 69 codons, they filed a second patent application.

c. AJM1 4.53-4.54: AJG1 7.30 - 7.31

3.41 Dr. Mattick declared as follows:

"In paragraph 2.7.18 Associate Professor Rogers states:

"...the claims directed to antagonists of VEGF-2 are not novel over prior art disclosures of forms of the receptors to which VEGF-2 could bind, but could not signal. See Document D27 (disclosing a dominant negative Flk-1 protein)."

"I can find no evidence in document D27 which establishes that the dominant negative Flk-1 protein described could bind VEGF-2. I observe that the dominant negative Flk-1 receptor described in D27 is created by deleting a significant portion of the intracellular kinase binding domain from part of one of the Flk-1 proteins that forms the receptor. Such a deletion may well inhibit binding of VEGF-2. In my opinion, no conclusions can be drawn from D27 about whether a dominant negative Flk-1 protein might serve as a VEGF-2 antagonist."
(AJM1 4.53-4.54.)

- 3.42 When Dr. Mattick quoted my first declaration, his cropping changed the context entirely. I prefaced the quoted remark with the statement, "Assuming *arguendo* that VEGF2 as taught in the specification possesses any biological activity that is mediated through cell surface receptors" VEGF and many other growth factors exert their activity through cell surface receptors. However, there is no evidence in the opposed application that VEGF2 acts as a growth factor for anything, or binds any receptors. That is why I prefaced my remark as I did.
- 3.43 Of course Dr. Mattick can find no evidence in document D27 to establish that VEGF2 binds Flk-1. As I explain in the preceding paragraph, there is no evidence even in the opposed application that VEGF2 binds any receptor or possesses any activity.
- 3.44 However, there is evidence from Dr. Alitalo's group that mature VEGF-C binds and exerts its activities through the receptors Flk-1/VEGFR-2 and Flt4/VEGFR-3. (See OPR1 at 4.11.1.3; Documents 70 and 71.) I raise Document D27 as prior art only if HGS's scientists continue to believe that VEGF2 molecules possess any biological activities mediated through one or both of these receptors.
- 3.45 Dr. Mattick's observation that a significant portion of the tyrosine kinase domain of Flk-1 was deleted to create the dominant negative mutant, and suggestion that the deletion "may well inhibit" binding of VEGF-2 is spurious. The ligand growth factors of Flk-1 are well known to bind the extracellular portion of Flk-1, and not the

intracellular tyrosine kinase domain that was deleted in Document D27 (see, for example, Chiang and Flanagan (Growth Factors 1995;12(1):1-10); Tessler *et al.* (J. Biol. Chem. 1994 Apr 29;269(17):12456-61) and Fuh *et al.* (J. Biol. Chem. 1998 May 1;273(13):11197-204), which are attached hereto as Exhibits PAWR-6, PAWR-7 and PAWR-8, respectively. It has been shown that VEGF-C molecules that can bind Flk-1 can bind a truncated version lacking the Flk-1 tyrosine kinase domain (see, for example, Document D71).

d. AJM1 4.55-4.60; AJG1 7.30 - 7.33

3.46 Dr. Mattick and Dr. Gamble declare that claim 50 is free of the prior art on the basis that the claimed antagonists must be "specific for" VEGF-2 polypeptides. (AJM1 4.56; AJG1 7.31) They misread the claim. Claim 50 is directed to an antagonist specific for the polypeptide according to any one of claims 28-48. I establish in my first declaration that claims 28-48 are not limited to VEGF-2 polypeptides, but rather, include prior art polypeptides as well. (See OPR1 at 2.7.9 and 2.7.11-2.7.15.) Because claims 28-48 are not restricted to VEGF2, the antagonist of claim 50 is not specific for VEGF2.

3.47 Dr. Mattick and Dr. Gamble misread claims 51-52 in the same way. (AJM1 4.57-4.58; AJG1 7.32-7.33) These claims are not limited to treating a patient with a VEGF-2 protein, but rather with "a polypeptide according to claim 28" or an antagonist thereof. Claim 28 reads on the prior art proteins and antagonists as well as on VEGF-2 (see OPR1 at 2.7.9), and consequently, claims 51-52 read on uses of the prior art proteins or antagonists, as I explain in my first declaration.

3.48 In paragraphs 4.59-4.60, Dr Mattick misreads claims 57-61 in the same way, because he believes that the earlier claims to which they refer are limited to VEGF-2 subject matter, which they are not. (See OPR1 at 2.7.21.)

e. AJG1 7.34 - 7.35

3.49 In paragraphs 7.34 - 7.35, Dr. Gamble appears to be responding to my explanation (in OPR1 2.7.20) that claim 56 encompasses the prior art. However, she only addresses

one observation regarding the absence of working examples. She does not dispute my analysis or conclusion regarding the claim encompassing the prior art.

F. Important uncontested aspects of my first declaration.

- 3.50 In Sections A-D, above, I explain that the arguments in support of novelty and invention provided by the HGS declarants are not persuasive because they do not relate to what was actually claimed, or because they rely upon unworkable claim interpretations, or other reasons. In Section E I address what I believe to be the only other arguments in support of novelty and invention provided by the HGS declarants.
- 3.51 To conclude my evaluation of the HGS evidence-in-answer as it relates to novelty and invention, I believe it is worthwhile to identify other uncontested points of my first declaration. In particular, there are many claims that introduce limitations not directly related to VEGF2, such as limitations relating to a heterologous polypeptide (claim 21); limitations relating to vectors, host cells, and methods of production (claims 22-27); limitations relating to use of pharmaceutical carriers (claim 53); limitations relating homo-dimerization (claim 47); and limitations relating glycosylation (claim 48). I explained in my first declaration that none of these claims/limitations confer novelty or invention to any claims that otherwise encompassed the prior art. (See, e.g., OPR1 at 2.7.7, 2.7.8, 2.7.10, 2.7.14, and 2.7.15.) I believe that none of the HGS declarants have contested these opinions expressed in my first declaration.
- 3.52 Many of the opinions that I offered in my first declaration relating to the issue of inventive step appear to have been uncontested by any HGS declarant. (See, e.g., OPR1 at 3.4 - 3.7.)

LACK OF FAIR BASIS AND INSUFFICIENCY

- 4.1 In Sections 4 and 5 of my first declaration (OPR1), I explained that the opposed application described an incomplete and non-working invention -- a description that was not adequate to practice the invention as claimed, and that certainly was not

commensurate in scope with the breadth of the claims that HGS was asking the Patent Office to grant to them. For example, I explained that there were defects in the application relating to the biological deposit and the description of experiments in the "Examples", and that the results reported in at least one example had been discredited in the scientific literature. I explained that "VEGF2" as taught in the opposed application was incomplete, could not be expressed and secreted as a protein as HGS had instructed in the opposed application, and that there was no evidence that the incomplete VEGF2 had any of the activity alleged in the application. The limited nature of HGS's contribution (sequencing of an (incomplete) cDNA, doing a database sequence comparison, and doing a Northern blot mRNA expression study) was not adequate to predict structure or function of the VEGF2 protein alleged as the invention. It certainly was not commensurate in scope with the amount of experimentation needed simply to make the invention work. I explained that the protein that the human body produces *in real life* from the VEGF2 gene has a structure vastly different from anything taught by HGS in the opposed application, and that the protein's principal function in adult tissues appears to be in regulation of the lymphatic system, a function that completely eluded the HGS inventors and was not suggested in the patent application. (The protein's structure and function were elucidated by Alitalo et al., a group that has since been awarded multiple patents on their work.) I explained that many of the HGS claims were not based on the application as it was filed, but rather, were an attempt to capture inventions such as those of Alitalo et al. that were published during the pendency of the opposed application before the Patent Office, but that owed nothing to the contributions embodied in the opposed application.

- 4.2 In this section of my declaration, I reply to the HGS evidence-in-answer that appears to relate to the issues of Lack of Fair Basis or Insufficiency. The declarations offered by HGS usually failed to identify which issue they were answering. Accordingly, I have attempted to reply to all such issues in a single section of this declaration.

A. ADMISSIONS AND UNCONTESTED EVIDENCE

A1. Admissions that the invention was incomplete.

4.3 Many of the HGS declarants have admitted for the record that VEGF2 as taught in the patent application is incomplete. Thus the opposed application did not provide the public with a complete invention. The HGS declarants admit that the beginning of the VEGF2 polynucleotide and polypeptide molecules, including the true VEGF2 signal sequence, was missing from the application as filed, and thus, that the teaching in the application that the first 24 of 350 amino acids represent a signal sequence, with mature VEGF2 being 326 amino acids, was simply incorrect.

4.3.1 Dr. Mattick: "the fact that the signal sequence information was incomplete"
(AJM1 at 4.13.)⁶

⁶Dr. Mattick admitted in his declaration that "An important difficulty that researchers faced in 1994 (and still face today) is the process of determining what a new gene encodes. This involves careful consideration and scientific training, and it is not a simple or straightforward process. Importantly, the isolation of a DNA sequence does not guarantee sufficient information to establish whether the sequence encodes a protein or if it does, the nature and function of the protein it might encode. Such information had to be determined in 1994 (as it is today) by a researcher using scientific skill, their experience, their knowledge and often a wide range of different analytical and experimental tools." (AJM1 at 3.13) Dr. Mattick declared that "once a DNA sequence had been cloned, further manipulations of that sequence would be relatively routine practice. Moreover once a protein sequence had been identified there were many routine methods available for analysing that protein." (AJM1 at 3.14.) When reading the declarations filed by HGS, it is important to remember that the inventors HAD NOT YET CLONED THE COMPLETE VEGF2 GENE. (In fact, the applicants filed a second patent application, more than a year later, when the inventors realized that the VEGF2 gene was incomplete.) Many of the techniques available for analyzing DNA and protein would have been fruitless if applied to VEGF2 taught in the opposed application, because VEGF2 was incomplete.

4.3.2 Dr. Gamble: "I note that a portion of the full length VEGF-2 sequence, which is not disclosed in the patent specification, is part of the NH₂ (amino) terminal end of the full length polypeptide sequence. This equates to 69 amino acids [The VEGF-2 signal] sequence is located among the 69 amino acids that were not disclosed in the patent specification." (AJG1 at 6.4.)

4.3.3 Dr. Hayward: "The patent specification discloses 350 amino acids of the VEGF-2 sequence whereas it has subsequently been determined that VEGF-2 has 419 amino acids. The missing amino acid sequence is now known to contain the signal sequence that directs secretion of VEGF-2 from the cell." (ANH1 at 3.13.)

4.3.4 Dr. Rapoport: "[T]he 350 amino acid form of VEGF2 corresponds to amino acid residues 70 to 419 of the 419 form of VEGF2." (ATR1 at 8).

4.4 Many of the HGS declarants then devote substantial material to explaining that they would have eventually experimented sufficiently to make alternate molecules-(e.g., foreign signal sequences attached to either a 350 amino acid VEGF2 or a 373 amino acid VEGF2) that the opposed application simply fails to teach. Such experimentation is beyond the teachings of the application, which is limited to relatively straight-forward partial cloning and sequencing work..

4.5 In fact, a strikingly large percentage of the evidence-in-answer is devoted to discussions of experiments that the declarants might have thought to have performed back in 1994, if provided with the teachings of the opposed patent application, in order to try to make or use the VEGF2 invention. I have tried to catalogue some of the numerous paragraphs in the evidence-in-answer devoted to such "obvious experimentation" to demonstrate its magnitude. (See Exhibit PAWR-9 to this declaration.) The extensive experimentation that HGS's experts would have needed

to perform validates my previous declaration setting forth that the opposed application lacks a disclosure adequate to place the public in possession of what is claimed as the invention. The large quantity of experimentation suggested, which the declarants for the most part have not actually performed to see if it would work, would not be needed at all if the invention worked in the manner described in the opposed application. I discuss some of the details of the proposed experiments further below.

- 4.6 Especially noteworthy is the large amount of experimentation devoted to figuring out that the application was wrong, and how to correct it. I explain in detail below that, even if all of the experimentation would have eventually resulted in a working invention, it would no longer be the invention of the opposed application. The experimentation suggested by HGS's declarations proceeds in a different direction.

A.2 Admission that VEGF2 is too distantly related to prior art molecules to reliably predict structure of function.

- 4.7 The opposed application is devoid of any evidence of VEGF2 activity. Instead, it predicts that VEGF2 will have the activities that others had shown for VEGF or for the PDGF's. In my first declaration I carefully explained that 22-30% amino acid identity between proteins would not have been considered sufficient to predict biological activity, and gave many examples. (See OPR1 at 4.6.3 - 4.6.5.) None of HGS's declarants explicitly disagreed with this position. In a statement that could be construed as partial agreement, Dr. Hayward declared "that there is not sufficient sequence identity between VEGF-2 and PDGF, VEGF and PIGF (as is clearly demonstrated in Figure 2) for these molecules to be considered derivatives of VEGF-2." (ANH1 at 3.8; see also ANH1 at 4.11 ("lack of detectable homology").

- 4.8 In fact, Dr. Gamble characterizes the homologies at the amino acid level between VEGF, PDGF α , PDGF β , and VEGF-2 as very low, with significant differences between the molecules, and very few stretches of significant contiguous amino acid sequences:

When regard is had to the information provided in the patent specification one observes that the homologies at the amino acid level between VEGF, PDGFa, PDGFb and VEGF-2 are very low. The identity between VEGF-2 and each of VEGF, PDGFa, PDGFb is 30%, 23% and 22% respectively (see page 5 of the patent specification). Further, there are very few contiguous sequences of amino acids that are identical between VEGF-2 and each of VEGF, PDGFa or PDGFb (see Figure 2 of the patent specification) In fact, the largest single contiguous sequence of amino acids is only seven amino acids in length and is found in the signature motif, which is identified by a box in Figure 2. After that stretch of residues there is one other stretch of six contiguous amino acids but no other significant contiguous amino acid sequences that share identity between VEGF-2 and VEGF, PDGFa or PDGFb. Thus, at the primary amino acid level there are significant differences between VEGF-2 and VEGF, PDGFa or PDGFb. (AJG1 7.13.)

- 4.9 I believe her characterization supports nicely the point that I made in my first declaration, that the low similarity and significant differences between VEGF2 and VEGF or the PDGF's would not permit reliable prediction of structure or function.
- 4.10 Similarly, Dr. Hayward says that "there is not sufficient sequence identity between VEGF-2 and PDGF, VEGF and PIGF (as is clearly demonstrated in Figure 2) for these molecules to be considered derivatives of VEGF-2." I interpret his statement to be an agreement that 22-30% sequence identity is too low for a person to have concluded that proteins would share the same function.

- 4.11 In my first declaration I explained that the examples in the application contained errors and omissions. (See, e.g., OPR1 at 4.13-4.13.5.) My analysis is essentially uncontested by the HGS declarants. In some instances, HGS's declarants confirm that there are errors and omissions. (See, e.g., ANH1 4.27; AJM1 4.90-4.92.)

B. MERE CATALOGUING IS NOT EVIDENCE AND DOES NOT ANSWER MY INITIAL CRITICISMS OF THE OPPOSED APPLICATIONS

- 4.12 Significant portions of the evidence-in-answer are devoted to highlighting the many general molecular biological techniques allegedly taught in the opposed application. (See, e.g., AJM1 at 3.12-3.19; 3.29, 3.31, 4.71; and 4.83; AJG 6.8-6.8.11; ANH1 at 3.6, 3.11, 3.21.) I acknowledged in my first declaration that the HGS application contains such "stock" teachings that HGS apparently chooses to include in many of its molecular biology patent applications, irrespective of the inventors and irrespective of the invention described and claimed. (OPR1 at 4.6.2.1.) I also set forth in detail many specific deficiencies of the opposed application which are not cured by regurgitation of standard molecular biological techniques. I maintain my opinion that the invitation in the opposed application to conduct further experimentation using standard molecular biological techniques does not cure the failure to adequately describe the VEGF2 invention in a manner commensurate with which HGS has attempted to claim it. No matter how much attention HGS draws to its stock teachings, they remain nothing more than an *invitation to experiment* and not a teaching of a complete VEGF2 invention. The amount of experimentation that HGS has left for the Australian public to perform in order to determine the true structure of the VEGF2 gene and protein, a working method of expressing and secreting the protein, and a proper identification of its biological activities vastly outweighs the amount of experimentation that HGS conducted before it filed its application on the incomplete VEGF2 gene. The experimentation is not merely routine work to make the invention work in the manner taught by the application. Rather, it is experimentation to discover something that is not described in the application, and how to make it work.

4.13 Significant portions of the evidence-in-answer are devoted to repetition of various predictions in the patent application that are unsupported in the application by scientific evidence, or even by a sound basis for prediction. I have attempted to catalogue some of these portions of the evidence-in-answer in Exhibit PAWR-10 to this declaration. I acknowledged in my first declaration that the HGS application contains such predictions. (OPR1 at 2.3.3 and 4.6.5.) I also set forth in detail that these were nothing more than predictions, lacking any apparent basis in scientific experiments. (OPR1 at 4.6.3.1 and 4.6.5.) I also set forth in detail that there was no accepted scientific basis for the predictions. (OPR1 at 4.6.3.1 and 4.6.5.) The evidence-in-opposition also included scientific evidence that many of the predictions were simply wrong. (OPR1 at 4.6.4 and 4.6.5.) The many specific deficiencies of the opposed application are not cured by regurgitation of the inventors' predictions in the evidence-in-answer, without critical evaluation of whether they have basis in fact. I maintain my opinion that the invitation in the opposed application to conduct further experimentation to determine how to make and use the invention, by seeing which (if any) predictions were correct does not cure the failure to adequately describe the VEGF2 invention in a manner commensurate with which HGS has attempted to claim it.

C. THE LARGE BODY OF EXPERIMENTATION EMBODIED IN THE HGS EVIDENCE CONCLUSIVELY PROVES THAT THE OPPOSED APPLICATION WAS INCOMPLETE AND INADEQUATE.

4.14 In this section I explain in greater detail that much of HGS's evidence-in-answer actually supports Ludwig Institute's opposition by confirming that the invention does not work as taught, and demonstrating that substantial experimentation and ingenuity would have been required to make the invention work. In many cases, the proposed experiments would have required ingenuity to contravene plain teachings in the application, after experimentally determining that the invention does not work as taught. In other cases, the ingenuity was of sufficient character that at least HGS believed that it warranted the filing of additional patent applications. In other cases,

the ingenuity was of sufficient character that other parties filed and were awarded patents on the work.

C1. Experimentation Needed to Make VEGF2 Polypeptides

- 4.15 I have reviewed the two declarations of Professor Alitalo where he performed controlled experiments to determine whether the approximately 350 amino acid VEGF2 taught in the opposed application can be expressed and secreted as a mature VEGF2 in the manner taught by the application.
- 4.16 In my opinion, Professor Alitalo's experiments were designed as an accurate reflection of what the patent application teaches to scientists in the field of the invention. The application teaches that the approximately 350 amino acid VEGF2 comprises a leader (signal) sequence of approximately 24 amino acids that would direct secretion of a mature VEGF2 of about 326 amino acids. Dr. Alitalo's experiments were designed to see if the encoding cDNA could be expressed and secreted as taught in the opposed application.
- 4.17 Dr. Alitalo's experimental results demonstrate that VEGF2 is not expressed and secreted as taught in the application. The design of the experiments was sound, and the results are clear. Knowing what we now know in year 2001 about VEGF2, an obvious explanation for the lack of expression is that the construct in the patent application lacks a signal peptide. The opposed application teaches an incorrect and nonfunctional signal peptide. It is not clear to me whether this error was ever brought to the Patent Office's attention before the opposition proceeding instituted by Ludwig Institute.
- 4.18 In fact, I think the declarations filed by HGS reflect silent recognition that the application was completely wrong about VEGF2, because the HGS declarants admit that the true signal peptide is missing, and then discuss alternative ways of expressing VEGF2 that are NOT taught in the application.

4.19. For example, Dr. Mattick admits “the fact that the signal sequence information was incomplete” at paragraph 4.13. In fact, he begins his detailed explanation of how he might have successfully expressed VEGF2 *with the assumption that an attempt to express the VEGF2 protein using the putative secretion signal sequence identified in the patent specification would not work.* (See AJM1 4.5, and ensuing discussion in paragraphs 4.6-4.13; see also AJM1 4.76-4.78.) In the ensuing discussion, Dr. Mattick goes on to explain how he would have deduced from the opposed application to express an approximately 373 amino acid VEGF2 sequence using a heterologous signal peptide (AJM1 4.7-4.8), even though he acknowledges in the very next paragraph that the application teaches only to attach a heterologous signal to “the mature sequence.” (AJM1 4.9)

4.20. The 373 amino acid construct that Dr. Mattick says that he would eventually have made is not described in the application at all. The application actually only teaches an approximately 350 amino acid full length VEGF2 and mature VEGF2 of 326 amino acids. Viewed in the manner most charitable to HGS, Dr. Mattick has said that, after determining (or being told) that the invention described in the patent application does not work, he might have been able to design some experiments to make an embodiment that is not described anywhere in the application, but that he thinks could work. And there is no indication that he has performed these experiments to see if they really do work.

4.21. Dr. Gamble makes the same admission as Dr. Mattick that the VEGF2 invention is incomplete: “I note that a portion of the full length VEGF-2 sequence, which is not disclosed in the patent specification, is part of the NH2 (amino) terminal end of the full length polypeptide sequence. This equates to 69 amino acids [The VEGF-2 signal] sequence is located among the 69 amino acids that were not disclosed in the patent specification.” (AJG1 at 6.4.) Like Dr. Mattick, Dr. Gamble assumes (with hindsight) that she would have had knowledge of this defect in the patent application, and explains that “The mere fact that the sequence disclosed in the patent application does not include the first 69 amino acids of the full-length VEGF-2 sequence would not dissuade me from attempting to express the sequence disclosed in the patent

specification with a heterologous signal sequence.” (AJG1 at 6.5.) Thus, Dr. Gamble apparently would have tried to attach a heterologous signal sequence to the approximately 350 amino acids of VEGF2 disclosed in the patent application. Dr. Hayward says he would have used a similar approach. (See ANH1 at 4.20.)

4.22 Dr. Hayward’s declaration of how he would have made VEGF2 polypeptides is redundant to the Gamble and Mattick declarations. Dr. Hayward, like Dr. Mattick and Dr. Gamble, admits that the VEGF2 taught in the patent application is incomplete, missing a large portion of the amino terminus which “is now known to contain the signal sequence” (ANH1 3.13.) Like Dr. Mattick, he says that he would have read the application as providing 373 amino acids, even though it explicitly states that VEGF2 is only 350. (ANH1 at 3.14.) Like Dr. Gamble, he says that he would have experimented and eventually attempted to express the 350 amino acids with a heterologous signal sequence, even though the application taught that the 350 amino acids already contained a signal sequence. (ANH1 at 3.20-3.26) Like Dr. Mattick, he says that if the 350 amino acid VEGF2 as taught in the patent application could not be expressed and secreted, then he would have begun experimenting to attempt to figure out what was wrong. (ANH1 at 3.17)

4.23 Dr. Rapoport provides a similar, redundant explanation. He says that all secreted proteins have easily recognizable signal sequences (ATR1 at 4-6), but does not see such a sequence in VEGF2 of the application. (ATR1 at 10.) Instead of concluding that VEGF2 is not secreted, he says he would have had great confidence that VEGF2 was secreted, and would therefore have attached a “strong” foreign signal sequence to 350 amino acid VEGF2. (ATR1 at 12.) He declares that “this approach is specifically taught in the HGS patent specification” at page 14, but it is not. Nothing in the opposed application would fairly be read to teach attaching a heterologous signal sequence to the portion of VEGF2 that was identified in the application as a signal sequence. Such signal peptide redundancy makes no sense when recombinantly expressing polypeptides.

- 4.24 The experimentation suggested by all of these declarants is not taught or even suggested by the opposed patent application, but rather is driven by hindsight knowledge of information published after the opposed application was filed. (See discussion below (subpart D) at paragraphs 4.55-4.66, repeated here by reference.)
- 4.25 Before leaving the topic of the VEGF2 expression experiments suggested by Drs. Mattick, Gamble, Hayward and Rappaport, I believe it is important to re-emphasize that they do not even attempt to reproduce the invention described in the opposed application. In fact, it is ironic that the four experts would read an application that taught mature VEGF2 is 326 amino acids, and then be motivated to make a construct comprising a foreign signal peptide attached to VEGF2 of 350 or 373 amino acids. The results of such experiments should have no bearing on the adequacy of the opposed application's teachings, because they are neither disclosed nor suggested in the opposed application. As I explain above, the approaches suggested by all of the HGS declarants reflect an unspoken admission that the invention does not work as taught in the opposed application. Whether or not the HGS declarants approve of Professor Alitalo's experiments described in his two declarations, they seem to recognize that his results are accurate, because they have abandoned the teachings of the application and are now advocating expression strategies that are not in the application.
- 4.26 Dr. Mattick, Dr. Gamble, Dr. Hayward and Dr. Rapoport all cite U.S. Patent No. 6,130,071, issued to Alitalo et al., as evidence that VEGF2 could be produced using the experimental approaches he has outlined in his declaration. (See AJM1 4.12; AJG1 6.5; ANH1 4.20; and ATR1 at 13)⁷ In my opinion, the Alitalo patent only serves as evidence that all of the extra work that the HGS declarants are describing is *inventive work by another*, and not routine work that should be credited to the opposed application of HGS. I observe in the "References Cited" portion of the

⁷Dr. Rapoport also relies on Dr. Alitalo's published journal articles, relating to VEGF-C. (See, ATR1 at 13-15).

relevant patent the citation of Documents D43, U.S. Patent Nos. 5,932,540, 5,935,820 (Documents D92 and Exhibit PAWR-11 respectively), and International Publication No. WO 95/24473 (Exhibit PAWR-12), all of which are related in some manner to the opposed application. In fact, WO 95/24473 appears to be identical to the opposed application. Ludwig Institute's attorneys have explained to me that, because these documents are listed in the "references cited" section, the documents were considered by the U.S. examiner when deciding to issue U.S. Patent No. 6,130,071. The fact that a U.S. patent examiner considered the invention of 6,130,071, filed in 1997, to be patentable after considering the contents of the opposed application (in the aforementioned documents), suggests to me that the work described in that patent is inventive work of others, and owes little or nothing to the teachings of the opposed application. Patented work of others can not reflect the efforts of routine experimentation.

4.27 Moreover, it is not clear to me how the content of U.S Patent No. 6,130,071 could be argued to support the adequacy of the disclosure of the opposed application in any way. The biologically active VEGF-C forms described in the 6,130,071 patent are NOT the 350 or 326 amino acid forms of VEGF2 taught in the opposed application. (Dr. Gamble represented to the Patent Office that they were in AJG1 6.5) Nor are they the 373 amino acid form that Dr. Mattick and Dr. Hayward believe they would have thought to create after reading the opposed application. Nor are activities such as Flt4 receptor stimulation or lymphatic endothelial cell growth factor of the Alitalo patent attributable to the opposed application. Dr. Rapoport premised his analysis on the "understanding that VEGF-2 and VEGF-C are terms used to refer to the same molecule." (ATR1 at 13). At least in the context of the present application, which taught an incomplete VEGF-2, and mistaught the mature molecule, this premise is clearly incorrect. (See paragraphs 2.13-2.16, above).

4.28 Also, it should be emphasized that Dr. Alitalo's research group had identified the full length 419 amino acid prepro-VEGF-C and had characterized its biological activities at the time that they filed their 1997 patent application and published their 1997

paper. The notion that this work should be credited to the opposed application, which taught an incomplete protein that is not expressed and secreted and that has never been reported in the literature to have any activity, is unacceptable.

4.29 Dr. Mattick declares that the VEGF2 sequence provided in the patent application "would have allowed me and I believe any person of ordinary skill in the field of molecular biology in 1994 to design specific strategies to obtain any polynucleotide sequence (ie gDNA, mRNA or cDNA) encoding VEGF-2." (AJM1 at 3.34) Dr. Hayward makes a similar declaration. (ANH1 at 3.26 and 4.18.) Of course, "designing strategies" is merely designing experiments for further research, and no guarantee of results. It is only necessary because the invention does not work the way that HGS taught in the opposed application. When HGS eventually isolated a full-length VEGF2 sequence of 419 amino acids, they thought the new result was significant enough to file a brand new series of patent applications. [See Documents D44-46 and discussion at OPR1 paragraphs 1.5.1.1-1.5.3.] If Dr. Mattick and Dr. Hayward think that "any" VEGF2 polynucleotide sequence was within routine reach by a person of ordinary skill, they are disagreeing with the inventiveness in HGS's second series of VEGF2 patent applications.

4.30 Dr. Mattick and Dr. Hayward also declare that the patent application's teachings regarding VEGF2 were sufficient to identify and isolate VEGF2 from other species. (See AJM1 4.93-4.94; ANH1 at 4.19.) The fact is, the teachings regarding VEGF2 are not even sufficient to provide the public with complete human VEGF2. (See OPR1 at, e.g., 1.5.1.1 and 4.11-4.11.1.3.) When HGS eventually discovered full length human VEGF2, they believed that the discovery was of sufficient magnitude to warrant another series of patent applications. (See Documents D44-D46.) It would have been a much greater leap from incomplete human VEGF2 to complete VEGF2 from other animals. Thus, I cannot agree with Dr. Mattick and Dr. Hayward's evaluation.

C2. Experimentation Regarding VEGF2 Biological Activity

- 4.31 The preceding paragraphs relate to all of the experimentation that HGS *admits* through its evidence in answer was necessary simply to express VEGF2 polypeptides.⁸ That is only *part* of the experimentation that would have been needed to practice the VEGF2 invention, because polypeptides *per se* are not necessarily useful for anything more than a curiosity for further research. It is equally clear from the evidence in answer that further experimentation was needed to figure out exactly what VEGF2 biological activity is. I originally discussed inadequacies of the teachings of the opposed application with respect to VEGF2 biological activity in OPR1 at 2.3.2, 2.7.4, 3.4.2, 4.6, 4.6.1-4.6.5, 4.8, 5.4, 5.5, and 5.9.
- 4.32 Dr. Mattick discusses VEGF2 biological activity at, e.g., AJM1 4.14-4.24. Dr. Gamble discusses VEGF2 biological activity at, e.g., AJG1 5.14-5.22, 6.7, 7.8-7.11, 7.15-7.18; and 7.28-7.29. Dr. Hayward discusses biological activity at, e.g., ANH1 at 3.6, 3.27-3.36, and 4.3-4.10.
- 4.33 In paragraph 4.15, Dr. Mattick selects ONE PASSAGE of the opposed application relating to *in vitro* expansion of vascular endothelial cells and says that he would have understood from it that an expected activity of VEGF-2 is to promote growth of vascular endothelial cells in culture. In paragraph 4.16 Dr. Mattick says that, "had I wanted to examine a secreted VEGF-2 protein using other assays relevant for activities specified in the patent specification (see below) I would have identified someone working in the vascular biology or endothelial biology field and I would have asked them for advice about the types of angiogenic assays that were available in 1994 and how to set up the assays, or I would have asked whether they would be prepared to collaborate with me in my research by testing the protein that I had produced." Dr. Gamble similarly selects testing for endothelial cell growth and/or angiogenic activity. (AJG1 5.14-5.22, 6.7, 7.8-7.11, 7.15-7.18, and 7.28-7.29.) Dr. Hayward selects these two functions and a few others. (See, e.g., ANH1 at 3.28-

⁸And, as I explain, the polypeptides that HGS's experts would make are not the one taught in the opposed application.

3.29.) Dr. Mattick says he could have used an endothelial growth activity to verify the production of VEGF2. Dr. Gamble says she could have tested VEGF2 activity with such an assay. Dr. Hayward says the testing would have been routine. I find several flaws in their analysis.

4.34 HINDSIGHT. As I explain in detail in my first declaration, endothelial cell growth is only one of a huge number of alleged uses for VEGF2 in the opposed application. Applying the reasoning of the HGS declarants, each one of the uses could have given rise to a number of activity assays. The HGS declarants apparently selected endothelial cell culturing because they (e.g., Dr. Mattick and Dr. Gamble) believe that HGS's subsequent work (e.g., embodied in the HGSII application, Documents D44-D46) shows that this is a valid activity.⁹ Even if endothelial cell growth were a true activity of VEGF2, there is nothing *in the opposed application* proving that endothelial cell culture is a good selection, as opposed to, e.g., a bone growth assay, a ligament growth assay, a cementum growth assay, or a collagen growth assay, just to name a few. (See opposed application at p. 17, first paragraph.)

4.35 Dr. Mattick alleges that VEGF2 activity for promoting growth of endothelial cells in culture has been validated:

“I note that such an activity has subsequently been shown to be something possessed by VEGF-2. I refer to HGS Patent Application 60467/96 (714,484), which shows that VEGF-2 exhibits proliferative effects on vascular endothelial cells (see page 42, line 32 to page 43 line 25 and Figures 8 and 9).” (AJM1 4.15)

4.36 Dr. Mattick should have, but failed to, qualify this remark by explaining that the VEGF2 purportedly tested in HGS's *second* VEGF2 patent application is a *different* VEGF2 than the VEGF2 that HGS taught in the opposed application. While Dr.

⁹This subsequent work related to polypeptides that were not taught in the opposed application and are not informative about the activity of VEGF2 polypeptides at issue in this proceeding. See paragraph 4.36.

Mattick may not think that this difference is significant, it appears to me that HGS felt that it was significant enough to warrant filing a second VEGF2 patent application. Drawing a conclusion about 326 amino acid mature VEGF2 taught in the opposed application based on data derived from what was allegedly an approximately 374 amino acid VEGF2 is precisely the type of scientific reasoning that HGS's declarants (e.g., Dr. Gamble) would rebuke as highly speculative. The excerpts cited by Dr. Mattick do not permit the conclusion that VEGF2 *taught in the opposed application* is useful for endothelial cell culture.

4.37 Dr. Mattick and Dr. Gamble cite no evidence whatsoever concerning the validation of an angiogenesis assay for the VEGF2 taught in the opposed application.

4.38 The only alleged scientific evidence of VEGF2 biological activity cited by Dr. Mattick, Dr. Gamble, or Dr. Hayward is in Example 1 of the application:

4.38.1 Dr. Mattick: "Further the patent specification provides in Example 1 Northern Blot data (see figure 4) showing that VEGF-2 is over-expressed in breast cancer cell lines. This result indicates to me that VEGF-2 is biologically active in tumours." (AJM1 at 4.18.)

4.38.2 Dr. Gamble: "... confirmation that the VEGF-2 sequence described in the specification is expressed in vivo, and therefore likely to indicate a biological activity, is provided in the Examples of the specification where it is shown by Northern blotting that a number of malignant breast tumour cell lines over express VEGF-2. The over expression of VEGF-2 in breast cancer cell lines while absent in a normal breast sample suggests a role of VEGF-2 in tumor development perhaps by promoting the growth of new blood vessels, as was observed for VEGF. (AJG1 7.17. See also AJG1 7.28 - 7.29)

4.38.3 Dr. Hayward: "In Example 1 in the patent specification the inventors demonstrate that VEGF-2 is over expressed *in vivo* in a number of malignant breast tumour cell lines. This result is, I believe, indicative of VEGF-2 biological activity. It suggests to me that VEGF-2 plays a role in tumour development possibly by promoting new blood vessel growth similar to VEGF. Additionally, it is apparent to me from reading the patent specification as I believe it would be to others in my field that VEGF-2 is a growth factor that is related to VEGF and is likely to play a role in the regulation of endothelial cell mitogenesis." (ANH1 at 4.6)

4.38.4 There are several problems with Dr. Mattick, Dr. Gamble, and Dr. Hayward's conclusions.

4.39 FAULTY EXPERIMENT. I explain in detail in my first declaration that the weight of published scientific experiments indicate that the gene that encodes VEGF2 produces an RNA message substantially bigger than 1.6 Kd, the size reported in Example 1. (See OPR at 4.13.1..) It is not clear to me that Example 1 even contains valid data.

4.40 WHAT IS THE VEGF2? Even if VEGF2 is active in tumors, Example 1 fails to address the question of what VEGF2 molecule we are talking about. The VEGF2 taught in the opposed application is incomplete, and I have never seen any published evidence that the incomplete VEGF2 is expressed and/or secreted in any human cells (healthy or cancerous). Dr. Alitalo's two declarations provide experimental evidence that VEGF2 as taught in the opposed application is not expressed and secreted by cells. Dr. Alitalo's published body of work relating to VEGF-C indicates that molecules very different from VEGF2 (as taught in the opposed application) are expressed *in vivo*. (See, e.g., Documents D71-D74.) Just because something might be happening with VEGF2 in tumors does not mean that the incomplete VEGF2 taught in the patent is involved. To the extent that a VEGF2-like molecule is

involved in breast cancer, the molecule might be the 419 amino acid VEGF2 that was the subject of HGS's second VEGF2 patent application, or the VEGF-C proteins that were the subject of Professor Alitalo's patent filings. A Northern hybridization study, even if performed correctly, would not indicate to a scientist what protein forms are present.

4.41 WHAT IS THE ACTIVITY? I shall assume in this paragraph that Dr. Mattick, Dr. Gamble, and Dr. Hayward are correct in concluding from Example 1 that VEGF2 is biologically active in tumors. Unfortunately, a scientist cannot say from a simple Northern hybridization experiment *what that activity actually is*. A correctly run Northern hybridization study tells a scientist whether a particular RNA is present in a sample, and possibly how much of that RNA is present in the sample. Without further experimentation, one cannot know whether the tumors are secreting VEGF2 as a growth factor for tumor cells (autocrine growth factor), or secreting VEGF2 to inhibit further growth of tumor cells, or secreting VEGF2 to stimulate or inhibit growth of some other tissue type, or secreting VEGF2 to kill nearby healthy cells to make room for tumor growth, or secreting VEGF2 to recruit some other cell type to the tumor, or secreting VEGF2 to inhibit immune cells such as tumor infiltrating lymphocytes from attacking the tumor, or any of a myriad of other activities. The scientific reality is that a Northern blot study provides only indirect evidence that a cell might be making a particular protein. It provides no evidence whatsoever as to what activity, if any, the protein is having. To paraphrase Dr. Gamble, any conclusion about VEGF2 activity from a Northern hybridization study, represents "pure speculation" and "cannot reasonably be drawn." Thus the example given in the application does not support the claimed activity.

4.42 In remaining paragraphs 4.19-4.24 Dr. Mattick does nothing more than catalogue the uses alleged for VEGF2 in the opposed application. In my first declaration I explained in detail that there is no sound scientific basis upon which these statements of activity were based or would be trusted by a practitioner in this field (OPR1 at 4.6.3.1 and 4.6.5.), and I repeat those explanations here by reference. As I explain above in paragraph 4.13, repeated here by reference, the cataloging of the activities in

a declaration does not make them more believable — there is still no evidence supporting them. This is precisely the scientific double standard that HGS is asking the public to accept in this proceeding. (See paragraphs 2.2-2.7 above, repeated here by reference.)

4.43 AJM1 Paragraph 4.23 provides a good example of the double standard:

“On page 24 (lines 25 to 31) the patent specification identifies uses of truncated versions of VEGF-2 for inactivating the activity of endogenous VEGF-2. It also discloses how such truncated molecules may be used therapeutically as anti-cancer drugs, to prevent inflammation or to treat solid tumour growth, diabetic retinopathy, psoriasis and rheumatoid arthritis (page 25 lines 4 to 13).” (AJM 4.23.)

The opposed application describes no polypeptides that are fragments of the approximately 326 amino acid mature VEGF2, and does not identify any polypeptides that were shown or believed to have VEGF2 inhibitory activity.¹⁰ Nor does the application provide any evidence that VEGF2 is involved in cancer in any way. Yet Dr. Mattick believes that the application discloses how truncated VEGF2 molecules may be used as anti-cancer drugs. Treatment of cancer continues to be one of the most researched and persistent problems of medical science, and has been for decades. There is no evidence in the opposed application to support this assertion. In my opinion, scientists with ordinary skill and experience, or higher, would not believe that fragments of a novel polypeptide could be used to treat cancer just because a

¹⁰ In paragraph 4.12 Dr. Mattick references “VEGF-C fragments” described in U.S. Patent No. 6,130,071 issued to Alitalo et al. These VEGF-C polypeptides were equated by Dr. Mattick with VEGF2 polypeptides, but of course they are not described in the opposed application and they are active polypeptides, not inhibitory ones.

patent application says so, when there is no disclosure of the activity of the polypeptide and no evidence of involvement of the polypeptides in cancer.

- 4.44 Dr. Hayward says that it is not reasonable to expect an initial characterization of a gene to provide "a full description, supported by detailed experimental proof, of every property and function that the encoded protein possesses." (ANH1 at 4.8) I agree with that position. However, if an inventor is seeking a patent on a gene, an encoded protein, a variety of "active" variants of the protein and gene, and a variety of uses of the protein and gene and variants, and other subject matter, then it is appropriate to ask the patent applicant to provide a working method for expressing and secreting the protein, and to provide evidence of some portion of the properties or functions. It is not appropriate to award the patent if the patent applicant has left for the public to determine how to make and how to use the invention. However, that is precisely the situation here, where the patent application has not shown how to express and secrete VEGF2 or demonstrated any function for VEGF2.

C3. Experimentation Relating to Inhibition of VEGF2 Activity

- 4.45 I originally discussed the inadequacies of the opposed application with respect to inhibition of VEGF2 activity in OPR1 at 6.6. Generally speaking, knowledge of a biological activity is a prerequisite to designing ways to inhibit the biological activity. Thus, all of the statements in my original declaration relating to biological activity, and all of the additional remarks on that subject above, are relevant to the lack of fair basis and lack of sufficiency regarding claims which pertain to inhibition of VEGF2.
- 4.46 AJM1 4.107 - 4.108. Dr. Mattick's remarks in support of inhibition or antagonism of VEGF2 are repetitious of his remarks relating to VEGF2 biological activity, which I discuss extensively above in Section C2 and repeat here by reference.

C4. Is VEGF2 a Lymphatic Growth Factor?

4.47 In my first declaration I discuss published evidence (largely from Professor Alitalo's group) that the principle activity of the real-life protein product of the "VEGF2 gene" in healthy mammals appears to be a growth factor for the lymphatic vessels.¹¹ This fact appears uncontested in HGS's evidence-in-answer.

4.48 It is also uncontroverted that, notwithstanding the numerous activities prophesied for VEGF2 in the opposed application, the inventors failed to teach that VEGF2 was a lymphatic growth factor. The big list of uses and activities that HGS taught, e.g., at page 16 of its application were simply copied from what other scientists had said about VEGF (See Document D36, U.S. Patent No. 5,219,739 beginning at col. 12, line 5 or PDGF.)

4.49 Dr. Mattick attempts to dismiss this shortcoming by drawing an analogy between characteristics of lymphatic vessels and blood vessels, perhaps implying that the opposed application was generic to both when it discusses endothelialization. (AJM1 4.74-4.75) However, he does not contest that the opposed application is completely silent about lymphatic growth or treatment of lymphatic disorders, and it is clear from the context of the alleged VEGF2 uses in the application that they were not contemplating uses relating to lymphatics. Although a bit crude, I would analogize Dr. Mattick's obscuring the distinction between blood vessels and lymphatic vessels to an auto mechanic obscuring the distinction between an auto's fuel lines and its cooling system. Both systems involve vessels (hoses) and liquid flows, but ordinary people in the field appreciate the significant differences in their functions.

C5. Experimentation Relating to "Examples"

4.50 In paragraph 4.13.1 of my first declaration, I explain that Example 1 of the opposed application has errors and inconsistencies, the most serious of which is that the results

¹¹ I also explain that the opposed application fails to teach the real-life protein product of the VEGF2 gene. [See OPR1 at 4.7.]

which were reported (VEGF2 mRNA of 1.6 kb/kd or 1.3 kb) are discredited by HGS's own subsequent work and work by at least two other independent research groups, which teach that the real mRNA is 2.2-2.4 kb in size. Dr. Mattick spends five paragraphs attempting to rehabilitate Example 1 for HGS (AJM1 4.84-4.88), but he does not contest the fact that HGS's experimental results are just plain wrong. The work reported in Example 1 misinformed the public about the identity and the size of VEGF2 mRNA.

4.51 In paragraph 4.13.2 - 4.13.3 of my first declaration I explain that Example 2 provides information of minimal value to understanding VEGF2 (4.13.2) and that the Example is full of errors and inaccuracies, and is incomplete. (4.13.3) The former is uncontested by Dr. Mattick. With respect to the errors, inaccuracies, and incompleteness, Dr. Mattick spends three paragraphs basically confirming my analysis, admitting that "there are a number of errors" (4.90); that descriptions are "inconsistent" with figures (4.91); that primers are misidentified or not identified at all (4.92); and the like. Dr. Mattick's attempt to rehabilitate the defective Example 2 is just another example of the scientific double standard being applied by HGS's declarants.

4.52 Dr. Hayward spends four paragraphs discussing Example 2 of the opposed application. (ANHI at 4.26-4.29.) He more or less confirms that Example 2 failed to teach the F5 primer, and that the F4 primer (part of primer pair 2) could not be used to make the polypeptide that was allegedly made. (Dr. Hayward's interpretations of these errors was that F4 as taught in the Example is really F5, and that F4 is missing.) Dr. Hayward declares that he would have been able to carry out experiments similar to those shown in Example 2, but that does not change the plain fact that Example 2 was described inadequately and it would have been left to the reader to experiment simply to try to repeat the "Examples" in the application.

C6. Summary Regarding Experimentation

4.53 To summarize, a large percentage of the evidence-in-answer is comprised of explanations of how the declarants, through experimentation, believe that they could have figured out that the opposed application was plain wrong in its characterization of VEGF2. And, after figuring out that the opposed application was wrong, the scientists believe that they could have performed additional experimentation to characterize VEGF2 correctly and then use it for whatever purposes their experimentation revealed VEGF2 could be used for. Thus, the evidence-in-answer appears to be advocating the position that HGS should be awarded a patent because the patent application would have created curiosity and enthusiasm to experiment, because with substantial experimentation one might have discovered the inaccuracies in the patent application, discovered that the invention does not work as described, and discovered alternatives or improvements that might have worked but that were not taught in the application. The question resolves to one of whether it is fair to grant a patent to the person that teaches an incomplete and incorrect invention that others might eventually be able to complete and use. In my opinion this is not fair. The merits of the patent application should be judged on what it teaches, and not how other scientists feel they could have overcome its substantial shortcomings and errors with experimentation. The fact that such experimentation might have revealed the inaccuracies in the opposed application or revealed alternative inventions to the invention described therein does not cure the errors or inadequacies of the application.

D. INAPPROPRIATE USE OF HINDSIGHT TO MISSTATE THE AMOUNT OF EXPERIMENTATION THAT WOULD HAVE BEEN NEEDED TO MAKE THE INVENTION WORK.

D1. Hindsight with respect to VEGF2 Expression.

4.54 I disagree with much of the evidence-in-answer because it is based on hindsight. In other words, the HGS declarants are drawing conclusions based on what is now known about VEGF2 and VEGF-C, based on papers and patents that were published after the filing date of the patent application. In this section I explain the hindsight

and provide a fairer analysis involving only the common general knowledge in 1994, combined with the teachings in the opposed application.

4.55 Dr. Mattick concludes that, even though VEGF2 as taught in the opposed patent contains only about 350 amino acids, “the nucleotide sequence disclosed in Figure 1 may also be read to encode an additional 23 amino acids.” (AJM1 at 3.22 and 4.7.) Dr. Hayward drew a similar conclusion. (ANH1 at 3.14 and 4.18.) As I explain below, Dr. Mattick’s and Dr. Hayward’s conclusion is contrary to the plain teachings of the opposed application. However, it is easy to see how they would have reached this conclusion when one considers documents published after the opposed application, which taught that VEGF2 includes additional amino acids. That is why their analysis is based on hindsight.

4.55.1 Figure 1 of the opposed application, to which Dr. Mattick and Dr. Hayward refer, depicts a DNA sequence and a deduced VEGF2 protein sequence. The opposed application explains Figure 1 as follows: “Fig. 1 depicts the polynucleotide sequence which encodes for VEGF2, and the corresponding deduced amino acid sequence of the full length VEGF2 polypeptide comprising 350 amino acid residues of which approximately the first 24 amino acids represent the leader.” (Opposed Application at p. 4, lines 28-32.) There is no ambiguity in the opposed application as to the length of full length VEGF2 or the location of the methionine amino acid at which full length VEGF2 begins.¹² And there is a clear statement identifying the

¹² The opposed application explicitly teaches that the methionine codon at the beginning of the VEGF2 protein-encoding sequence is at approximately positions 71-73 of the DNA sequence in Figure 1. The relationship between a polypeptide and the DNA coding sequence encoding it is a relationship of tri-nucleotide codons: each amino acid is encoded by three nucleotide “codon” units. The DNA strands (chromosomes) that characterize the human genome each comprise hundreds or thousands of protein coding sequences, generally

inventor's belief in the division between the 24 amino acid signal peptide and the "mature" VEGF2 of 326 amino acids.

4.55.2 As I explained in my first declaration, multiple groups, including the very inventors of the opposed application, later refuted the notion that the protein encoded by the VEGF2 gene is only about 350 amino acids. It is, in fact, about 419 amino acids, but the opposed application failed to teach about 69 amino acids at the beginning of the protein. [See OPR1 at 4.11.1-4.11.3 (citing Documents D43, D44-46, D84-86 of HGS; D75 and D84 of Genentech; and D71-D74 of University of Helsinki.)]¹³

4.55.3 Thus, it is easy to understand how Dr. Mattick or Dr. Hayward could have used hindsight to conclude that the Figure 1 sequence might actually encode more than 350 amino acids, because numerous publications from about 1996-2001 reported this. But the conclusion is clearly biased on what is now known in year 2001, and contrary to the plain teachings of the opposed application.

4.56 Dr. Mattick compounds this hindsight by opining that he would have learned from the patent application to express VEGF2 with these extra 23 amino acids:

Taking into account the existence of the additional 23 amino acids at the N-terminal end of the VEGF-2 sequence disclosed in the patent specification, I would also have stitched a signal secretion sequence to the

separated by stretches of non-coding sequences. Each protein coding sequence begins with the codon ATG, which encodes methionine.

¹³Interestingly, the 373 amino acid VEGF2, which has no basis in the application, also has no apparent significance in human biology. The HGS declarants have acknowledged that the full length VEGF2 (with signal sequence) is actually 419 amino acids. The Alitalo research group has shown that the 373 amino acid molecule is vastly different than the forms of protein secreted by human cells.

beginning of the cDNA disclosed in the patent specification, as is taught in the patent specification. I note that such an experiment was done and is described in Australian Patent Application 60467/96 (714,484) (HGS' second VEGF-2 patent application) and the resultant product from those experiments is reported to be biologically active (see page 42, line 32 to page 43 line 25 and Figures 8 and 9 -- HGS' second VEGF-2 patent application). (AJM1 4.8)

4.57 The hindsight knowledge of the "additional 23 amino acids" that are not taught in the application is compounded here by a hindsight knowledge gained from HGS's second VEGF2 application to attach a signal peptide to the beginning of the additional 23 amino acids. To the extent the opposed application suggests attaching a foreign signal peptide to a VEGF2 sequence, the suggestion would have been to attach it to "mature VEGF2" which comprised only about 326 amino acids (see opposed application at pp. 4-7). It would have been highly irregular to attempt to attach a signal peptide-encoding sequence to what was taught to be 69 nucleotides of noncoding sequence, because signal sequences are not ordinarily used to drive expression of noncoding sequences. This is especially true when the patent application taught that a true signal sequence immediately followed the 69 nucleotides of noncoding sequence. (Polypeptides don't need two signal peptides for expression and secretion.)

4.58 Dr. Mattick devotes three pages to explaining how he would have expressed VEGF2 using "routine trial and experimentation." However, Dr. Mattick has used hindsight in his explanation because his explanation *begins* from the following assumption:

"Had I attempted to express the VEGF-2 protein using the putative secretion signal sequence identified in the patent specification and had that not worked"

(AJM1 4.5.)

- 4.59 Dr. Hayward begins his analysis from a similar vantage point. (See ANH1 at 3.17.) The HGS declarants start here because, with hindsight knowledge, they know that the signal sequence taught in the opposed application does not work. However, at the time the patent application was filed, scientists with ordinary knowledge presumably would not have known that the signal sequence taught in the application would not work. Such scientists would have read the teachings in the application concerning the sequence listing, tried to express the polypeptide according to the application, and failed. Then, the person might have repeated his experiment and modified any of a number of parameters (cell type, expression vector, promoter, growth conditions, and so on) to try to discover why things did not work. Extensive experimentation might have been necessary before arriving at the true source of the problem and solution.
- 4.60 A similar analysis applies to the manner that most of the other HGS declarants say that they would have successfully expressed and secreted a VEGF2 polypeptide. At least Drs. Gamble, Dr. Hayward, and Dr. Rapoport say that, even though the VEGF2 taught in the patent application is incomplete and the portion of the sequence described as the signal is incorrect, they would have expected to be able to successfully express and secrete VEGF2 by attaching a heterologous (foreign) signal sequence to the 350 amino acids of VEGF2 that were taught in the patent application. (See AJG1 at 6.5; ANH1 at 3.20-3.22; ATR1 at 13.) Dr. Power reported that she performed such an experiment (ASP1), and Dr. Aaronson spoke approvingly of that experiment. (See, e.g., ASA1 at 15-22).
- 4.61 The notion of expressing the 350 amino acid VEGF2 taught in the opposed application with a heterologous (foreign) signal peptide may be an interesting scientific curiosity, but it has nothing to do with the teachings in the opposed patent application. The opposed application teaches the reader that the VEGF2 of about 350 amino acids *already* consists of a leader sequence (i.e., a signal sequence) representing the first approximately 24 amino acids, and a mature protein of 326 amino acids. (See, e.g., page 5 of opposed application.) Scientists in 1994 or today would not have had any reason to express a protein that already contained a signal sequence using a method that involved attaching a heterologous (foreign) signal

sequence (e.g., Dr. Power's Ig Kappa signal sequence) to the beginning of the natural signal sequence. Such an experiment is not a replication of any example in the opposed application or a reasonable extension of any of its teachings. The instructions that HGS gave to Dr. Power for her experiments were not to replicate the teachings of the opposed application. (See ASP1 at 2.) One might infer that HGS gave these instructions because they knew that the invention taught in the patent application does not work the way that they said it would. (Dr. Alitalo's first declaration (OKA1) showed this.) And the suggestion by the HGS declarants that they would have identified the cause of the failure without extensive experimentation is based on the hindsight knowledge of what they now believe will work.

4.62 The only suggestion to perform the experiment of attaching a heterologous (foreign) signal sequence to the 350 amino acid VEGF2 comes from scientific and patent literature regarding VEGF-C or VEGF2 that was published after the filing date of the opposed application. When one reads that literature, one learns that the gene in actuality has 419 codons, and that the 350 codon sequence was incomplete and lacked a signal peptide. (See OPR1 at, e.g., 1.5.1.1 and 4.11-4.11.1.3; ATR1 at 8.) One also learns (from the VEGF-C literature) which forms of the molecule have biological functions, such as stimulation of the lymphatic system. Even if the experiments involving a heterologous sequence in combination with 350 amino acid VEGF2 work, the results should not be credited to the opposed application, but rather, to the ingenuity of others who determined that VEGF2 does not work in the manner described in the opposed application, but works in a totally different manner.

4.63 Dr. Rapoport's analysis of the signal peptide issue also suffers from hindsight. For example, Dr. Rapoport declares that it was known that signal sequences located at the N-terminus of proteins "were required to directed secreted proteins outside of the cell." (ATR1 at 4-5). He says that researchers were able to characterize such sequences by inspection or with software. (ATR1 at 5-6). Dr. Rapoport says that he fails to observe a typical conserved motif of a signal sequence in the 350 amino acid VEGF2 taught in the opposed application. (ATR1 at 10.) Given what he says about signal sequences in paragraphs 4-6, one might have expected Dr. Rapoport to

conclude that VEGF2 was not secreted at all. (That would have been a logical inference to make about a protein that does not appear to have a signal sequence.)

4.64 Instead, Dr. Rapoport says that there was "strong evidence" that the 350 amino acid VEGF2 was a secreted protein "based on the teaching and recognition of the HGS specification that it is a member of a family of secreted growth factors." (ATR1 at 10 and 7.)

4.65 However, the "strong evidence" upon which Dr. Rapoport relies does not withstand scrutiny. The only "evidence" is the recognition that VEGF2 exhibited 22-30% identity with VEGF and the PDGF proteins. (ATR1 at 7, 9.) I explained in detail in my first declaration that this low level of sequence identity does not permit reliable prediction of structure or function. (See OPR1 at 4.63-4.65.) That portion of my first declaration was not contested by any HGS declarant. There are many examples in the literature of proteins with significantly greater structural similarity, but divergent function. In fact, the examples in my first declaration demonstrate that 22-30% sequence similarity is not even sufficient to be sure that two proteins are both growth factors, or are both secreted from cells. Here are two more examples directly relevant to the field of blood vessel growth:

4.65.1 The angiopoietins comprise a "family" of proteins believed to modulate endothelial cell growth in humans. Although angiopoietins share amino acid identity of, e.g., about 40-70%, some family members appear to stimulate receptors involved in endothelial cell growth, whereas others appear to antagonize (block) them. Thus, angiopoietins share greater sequence similarity with each other than VEGF2 shares with VEGF, but angiopoietins can have directly opposing activities towards each other, with some being growth factors and others being growth factor antagonists.

4.65.2 The fibroblast growth factors (FGF's) comprise another "family" of growth factors. Some, but not all, members of this family have signal peptides for directing secretion of the protein from cells. The FGF's demonstrate that not

all proteins in a particular protein "family" can be expected to have a traditional signal sequence.

4.66 In fact, even if there were sufficient evidence in the opposed application to conclude that VEGF2 were a growth factor, it is untrue that all growth factors are secreted. The ephrins represent yet another "family" of proteins, that like VEGF, have members that appear to play a role in vascular development and interact with their own receptor tyrosine kinases (known as the Eph receptors). All known ephrins are tethered naturally to the cells in which they are expressed, and must normally remain attached to the cell membrane to activate their receptors or other cells. Ephrins B1-B3 all have transmembrane and cytoplasmic domains that localize in the cell's membrane and cytoplasm (interior), respectively.

4.67 The foregoing examples and the uncontested examples from my first declaration demonstrate that Dr. Rapoport had no "strong evidence" upon which he could base his conclusions, except for hindsight knowledge gained from the reported work of HGS's competitors.

4.68 In my opinion, the only true motivation for the research that Dr. Rapoport describes involving foreign signal peptides attached to 350 amino acid VEGF2 comes from knowledge of the 419 amino acid VEGF2 (ATR1 at 8) and published information about VEGF-C (ATR1 at 13-17.) The allegations about what he would have recognized, predicted, and/or expected based solely on the application do not withstand scrutiny.

D2. Hindsight with respect to VEGF2 biological activity.

4.69 I discuss Dr. Mattick's and Dr. Gamble's hindsight with respect to VEGF2 biological activity above in paragraphs 4.27-4.40 which I repeat here by reference.

4.70 Dr. Hayward also exercises hindsight in his discussions of VEGF2 biological activity. (See, e.g., ANH1 at 3.6; 3.27-3.36.) He explains that he understands VEGF2 activity

to mean one select list of functions that are recited in the opposed application (such as angiogenesis or promoting endothelialisation or wound healing) but fails to list other functions, such as growth of damaged bone, periodontium, or ligament tissue as stated at page 17 of the opposed application. (See, e.g., ANH1 at 3.6; 3.28.)

- 4.71 Dr. Hayward also exercises hindsight by declaring that one of ordinary skill would have considered whether VEGF2 bound to Flt1, Flk1, and Flt4. (See ANH1 at 3.30 - 3.35.) Receptor tyrosine kinases (RTK's) serve as receptors for a large number of molecules, including the PDGF's. My current scientific work includes RTK and RTK inhibitor research, and in my estimation the human genome contains perhaps 500 to 1000 different RTK's (only a small fraction of which would have been characterized in 1994). The suggestion that a person would have focused on only those three receptors (Flt1, Flk1, and Flt4) is based on hindsight knowledge that fully processed VEGF-C was shown by Alitalo et al. to bind to two of them. The idea to screen Flt4 or other particular receptors is not found in the application.

E. CLAIMS WHICH RECITE PARTICULAR SUBSETS OF THE VEGF2 SEQUENCE LACK FAIR BASIS AND LACK SUFFICIENCY. REPLY TO AJM1 4.96-4.102 AND AJG 6.8.1-6.8.2.

- 4.72 In paragraph 5.8.1 - 5.8.6 of my declaration I explained that the opposed application as written provided no indication that the applicants intended to claim the particular sequences of claims 11-12, 32-35, and 40-41, and that the only mention of these portions of VEGF2 were not as peptides, but rather, were as observations that they represented portions sharing conserved motifs with the prior art. Dr. Mattick gleans such an intention from identification of the conserved motifs at page 5 and Figure 2, in combination with the teaching at page 9 about "fragments of VEGF-2." I am not persuaded by this analysis.

- 4.73 When I read the discussion of page 9 concerning fragments, I see no mention whatsoever of conserved motifs or of the alleged "signature" sequence. When I read page 5 and Figure 2, I see a discussion of the signature motifs but no mention of

VEGF2 fragments of the invention. I only see an observation that VEGF2 shares two attributes with VEGF and PDGF, and neither attribute is actually a VEGF2 "fragment."¹⁴ Nowhere in the application is the "signature for the PDGF/VEGF family" stated to represent a "VEGF2 fragment" of the invention.

4.74 Dr. Mattick apparently does not dispute my conclusion that claim 31 is entirely unsupported in the application. (See OPR1 at 5.8.7), or my observations in paragraph 5.8.9 regarding failure to adequately teach VEGF2 "activity" information about these peptides, even if they were adequately described.

4.75 In paragraph 6.8.1 - 6.8.2 Dr. Gamble summarily states that she believes that the patent specification provides "a range of different length VEGF-2 polypeptides." as well as the DNAs encoding them. For reasons explained in my first declaration and in the preceding paragraphs, I disagree.

F. LACK OF FAIR BASIS OR SUFFICIENCY FOR VEGF2 MRNA.

4.76 In AJM1 4.103 - 4.104, Dr. Mattick responds to my criticism in OPR 5.8.10 that the opposed application lacks support for VEGF2 mRNA because the alleged mRNA in the opposed application is clearly misidentified. Dr. Mattick cites Example 1 as providing support for VEGF2 mRNA. Dr. Hayward provides analysis of Example 1 at ANH1 paragraphs 4.21-4.24.

4.77 I am unpersuaded by Dr. Mattick's and Dr. Hayward's analysis. I note apologetically that OPR 5.8.10 should have referred to Example 1 in the opposed application, rather than Example 2. A review of Example 1 proves my original point. In paragraph 4.13.1 of my first declaration, I explained that Example 1 of the opposed application

¹⁴ What I mean by this is that the first attribute - eight conserved cysteines - are scattered throughout the VEGF2 sequence, not a fragment of it. The second attribute is a generic chemical formula PXCXXXXRCXGCCN, not a VEGF2 fragment.

has errors and inconsistencies, the most serious of which is that the results which were reported (VEGF2 mRNA of 1.6 kb/kd or 1.3 kb) are *discredited by HGS's own subsequent work and work by at least two other independent research groups*, which teach that the real mRNA is 2.2-2.4 kb in size. Dr. Mattick relies on Example 1 and spends many paragraphs attempting to rehabilitate Example 1 for HGS (AJM1 4.84-4.88, 4.104), but he does not contest the fact that HGS's experimental results are *just plain wrong*. The work reported in Example 1 misinformed the public about the identity and the size of VEGF2 mRNA.

4.78 Dr. Hayward also does not contest that the 1.6 kb/kd result reported in Example 1 and relied upon by the HGS declarants in various aspects of their declaration is wrong, and discredited by subsequent experiments. However, Dr. Hayward attempts to rehabilitate Example 1 by interpreting a different experimental result, namely Figure 5. Dr. Hayward says that he would judge Figure 5 as showing a band of about 2.4/2.3 kb and a band of 1.6 to 1.8 kb and that "at least the major band is reasonably consistent with subsequent results." (ANH1 4.24).

4.79 Whatever meaning Dr. Hayward can now discern from Figure 5 does not change the fact that HGS attributed no significance to Figure 5 whatsoever when it wrote the opposed application. Nor does his interpretation change the fact that the result upon which the inventors told the public to focus, 1.6 kb/kD, is now discredited.

4.80 Moreover, it's not clear to me that Dr. Hayward's interpretation of Figure 5 is even reliable. He admits that there is at least one mislabeled band (ANH1 at 4.24-4.25) and it appears to me that there may be more than one mislabeled band. There is no basis in the application to determine which of the band inconsistencies in Figure 5 are right or wrong (or whether all are wrong).

G. THE PATENT APPLICATION MIS-TAUGHT VEGF2 PROTEOLYTIC PROCESSING.

- 4.81 Dr. Gamble devotes several pages of her declaration discussing knowledge of prior art growth factors PDGFs, VEGF, and PlGF, including discussion of proteolytic processing of these proteins. (See AJG1 5.1-5.13.) Her apparent reason for the lengthy discussion of the prior art is an attempt to rehabilitate the teachings of the opposed application relating to VEGF2. (See AJG1 6.1 - 6.5; 7.23-7.24.) Dr. Rapoport's declaration also relies heavily on analogy to VEGF and PDGFs processing for his declaration. (See, e.g., ATR1 at 7, 9, and 11.)
- 4.82 First, it is important to remember that the opposed application taught an incomplete VEGF2 sequence, missing about 69 codons/amino acids. At least three of HGS's declarants have admitted this important omission from the patent application. (See paragraphs 4.3-4.3.4 above, repeated by reference.)
- 4.83 When assessing the sufficiency of the opposed application, it is also important to bear in mind its actual teachings. The opposed application taught the inventors' best prediction at the time regarding proteolytic processing (i.e., signal peptide of 24 amino acids, mature protein of 326 amino acids), which was plain wrong. Dr. Alitalo's two declarations confirm that cells cannot express and secrete VEGF2 taught in the patent application. (See Dr. Alitalo's declarations, OKA1 and OKA2.)
- 4.84 Knowledge of the proteolytic processing of prior art proteins, discussed extensively by many of the HGS declarants, does not support patentability. If anything, it negates it. The HGS inventors used knowledge of prior art proteins (e.g., VEGF) to predict the signal peptide and mature portions of VEGF2 in their patent application, which is essentially what the HGS declarants say that they would have done. (See AJG1 6.5: "Thus, I would predict that VEGF-2 would be expressed in a similar way." See also AJG1 6.10 - 6.11; ANH1 at 3.15; ATR1 at 11: "I would predict VEGF-2 to be expressed in a similar way [as the PDGF/VEGF family of growth factors'.") HGS was plain wrong in the opposed application, and HGS's declarants likewise would have been wrong in their prediction. The processing taught by the opposed application (simple removal of a signal peptide at position 1-24) does not occur. (See OKA1 and OKA2.)

4.85 Moreover, the full length 419 amino acid protein (VEGF-C) is processed in a manner unexpectedly different and more complex, compared to simple removal of a signal peptide. (See OPR1 at 4.11.1.3 and Documents D70, D71, D73, and D74 cited therein.) Therefore, I must disagree with Dr. Gamble's suggestion that "VEGF-2 is no different in that it contains a signal or leader sequence." (See AJG1 at 6.4; see also AJG1 at 6.3) The processing of the full length VEGF-C protein is substantially different. Even when HGS discovered the 419 amino acid VEGF2 sequence and filed its second patent application, they still badly mis-predicted the manner in which the protein is processed.¹⁵

4.86 Thus, the only relevant portion of Dr. Gamble's declaration or the other declarations relating to proteolytic processing is her admission that the opposed application was incomplete. She plainly agrees that the VEGF2 signal/leader sequence "is located among the 69 amino acids that were not disclosed in the patent specification." (AJG1 6.4 (emphasis added).)

4.87 In paragraph 7.24, Dr. Gamble declared as follows:

I was aware that all members of the PDGF/VEGF family (known in March 1994) underwent some proteolytic processing when produced from a cell. Thus, had I been asked to examine VEGF-2 in March 1994 I would have expected that VEGF-2 may also naturally undergo some proteolytic processing when released from a cell. This process occurs naturally during secretion, controlled by cellular enzymes. Consequently, if a

¹⁵ In its second generation VEGF2 patent applications, Human Genome Sciences taught that 419 residue VEGF2 has putative leader sequence of approximately 23 residues such that the mature protein comprises 396 amino acids (See Document: D43 and D44 at p. 7, last paragraph). In fact, the leader is 31 amino acids, and the mature protein is much smaller due to additional proteolytic processing. See Document D71.

researcher were able to produce VEGF-2 and secrete it from a cell I believe a reasonable expectation would be that processing would take place. Therefore, in my opinion, the patent specification fully enables one to express and secrete a biologically active protein that has been correctly processed.

- 4.88 Dr. Gamble's qualifier "if a researcher were able to produce VEGF2 and secrete it from a cell" cannot be overemphasized, because Dr. Alitalo has shown that VEGF2 as taught in the patent application is not expressed and secreted. Her statements about "reasonable expectation" are really "pure speculation and cannot reasonably be drawn" (see AJG1 7.52.)

H. THE FACT THAT HGS's DECLARANTS WOULD HAVE MADE THE SAME MISTAKES AS THE HGS INVENTORS DOES NOT REHABILITATE THE OPPOSED APPLICATION

- 4.89 Dr. Aaronson briefly explains that, had he been presented with a novel 350 amino acid VEGF2 sequence in March 1994, he would have (a) predicted that it was proteolytically processed; and (b) predicted that it was biologically active. (See ASA1 at 5 - 6.) Dr. Gamble makes similar predictions. (See AJG1 at 6.5.) In my opinion, what should matter is whether or not the application is correct, and not whether Dr. Aaronson or anyone else would have made favorable or unfavorable "predictions."
- 4.90 Processing: As I discuss in detail in the preceding section, the HGS scientists also predicted proteolytic processing in a manner analogous to VEGF. (See paragraphs 4.71-4.75.) The important point is that they were wrong, and what they taught the public in the opposed application was wrong. First, the VEGF2 was incomplete, and is not processed by cells in the way that Dr. Aaronson or the HGS inventors predicted. Second, even when the full 419 amino acid VEGF2 was discovered by the HGS inventors much later, they still predicted wrong. Dr. Alitalo's science has shown that the proteolytic processing of VEGF-C is much more complicated than the proteolytic processing that occurs with VEGF. See Document D71.

4.91 Activity: There is still no evidence in the patent application or the ensuing literature of the next seven years that has been made of record in this proceeding that the VEGF2 taught in the *opposed application* is "biologically active." HGS's declarants believe that the requisite testing for activity would have been "routine" (see, e.g., ANH1 at 4.7), but HGS has only reported activity data for molecules that were taught in its *second generation* application or molecules taught by *other research groups* (e.g., Alitalo et al. for VEGF-C) that differ from VEGF2 of the opposed application.

I. THE EVIDENCE OFFERED BY HGS IN SUPPORT OF THE OPPOSED APPLICATION RELATES TO A DIFFERENT INVENTION THAN THE ONE TAUGHT IN THE APPLICATION.

4.92 In this section I explain that the important data and opinions offered by HGS in its evidence in answer does not actually relate to the invention of the opposed application. Rather, it relates to subsequent inventions.

4.93 The teachings in the opposed application concerning full length and mature VEGF2 are unequivocal: "The polynucleotide of the invention . . . contains an open reading from encoding a protein of about 350 amino acid residues of which approximately the first 24 amino acid residues are likely to be leader sequence such that the mature protein comprises 326 amino acids"

4.94 Notwithstanding these clear teachings, HGS has devoted a vast portion of its declaration evidence arguing about the merits of totally different VEGF2 proteins that were not taught in the application.

4.95 For example, HGS asked Dr. Power to treat the 350 amino acid VEGF2 as "mature VEGF2" and try to express it by attaching a different signal sequence to it: "The Patent Attorneys for Human Genome Sciences (HGS) requested that I perform the following experiments in order to determine whether the 350 amino acid form of VEGF-2 (corresponding to residues 70 to 419 of the 419 amino acid form of VEGF-

2) fused in frame with a heterologous signal sequence would result in the expression and secretion of the protein from eukaryotic cells.” (ASP1 at 2.)

- 4.96 Dr. Aaronson cited Dr. Powers work expressing a 350 amino acid VEGF2 with a different signal sequence with approval. (See ASA1 at 15 - 22.)¹⁶ Dr. Gamble endorsed the same approach for “attempting to express” the VEGF2 sequence which she noted, with hindsight, was missing the real VEGF2 signal sequence. (AJG1 6.4-6.5.)
- 4.97 Dr. Mattick was even more creative in declaring that he would have been motivated to express a 373 amino acid VEGF2 with a different signal peptide. (See discussion herein at paragraphs 4.19-4.20.) Dr. Hayward came down somewhere in between, because he agreed with Dr. Mattick that he could find 373 amino acids supported in the application, but he then discusses how he might have attempted to express the 350 amino acid VEGF2. (ANH1 3.13-3.26)
- 4.98 These hypothetical experiments (real experiments in the case of Dr. Power) may be interesting to consider, but they have nothing to do with what the opposed application taught the public, because it taught the public that mature VEGF2 was 326 amino acids.
- 4.99 One explanation given by the HGS experts for their creative approaches was that the opposed application taught that one could express VEGF2 using a heterologous leader sequence. See ASA1 at 16; AJM1 at 4.9. However, a scientist of ordinary skill who desires to express a secreted protein using a heterologous leader sequence will use the heterologous leader to *replace* the native leader sequence. (For example, replace amino acids 1-24 of VEGF2 with a heterologous leader sequence, attached to

¹⁶ Dr. Aaronson declared that Dr. Power succeeded in producing “a biologically active” protein. (See ASA1 17.) I dispute this characterization. Dr. Power did not report any activity assay data in her declaration. She reported only an expression study.

positions 25-350.) There is nothing in the opposed application teaching that one should substitute a heterologous leader to the 350 amino acid VEGF2.

- 4.100 The inference that could be drawn from all of this is that neither HGS (who designed Dr. Power's experiments) nor its declarants believe in the 326 amino acid mature VEGF2 taught by the opposed application.
- 4.101 Dr. Hayward declares that he is aware that VEGF2 is proteolytically processed upon secretion from cells in vivo to form the naturally occurring ligand for the Flt4 and KDR/Flk-1 receptors. (ANH1 at 3.22. See also ANH1 at 3.30- 3.35.) He is mistaken. As I explain in my original declaration (OPR1 at 2.7.18) and again above (e.g., Paragraph 2.15), fully processed VEGF-C, invented and patented by Alitalo et al. (see, e.g., U.S. Patent Nos. 6,221,839 and 6,245,530, Exhibit PAWR-13 and Exhibit PAWR-14, respectively), is a ligand for Flt4 and KDR/Flk-1. The 350 amino acid VEGF2 as taught in the original application was not taught to be a ligand for any receptor, cannot be expressed and secreted by cells, and has never been reported in the literature to be a ligand for these receptors.
- 4.102 Dr. Hayward also declares that VEGF-2 "of course" functions as a growth factor. This, too, has never been established. The VEGF-C forms invented by Professor Alitalo's group have been reported to have certain growth factor activities, and the HGS II application alleges that some unidentified form of VEGF2 may have exhibited some growth factor activity in some experiments. However, the VEGF-C polypeptides of Alitalo and the 419 amino acid VEGF2 from the HGS II application are not the teachings of the opposed application.
- 4.103 Dr. Hayward also declares, "page 4 lines 12 to 14 of the patent specification states that the VEGF-2 polypeptides of the invention may be used to isolate receptors of VEGF-2. At page 24 fifth paragraph to page 25 first paragraph the patent specification discloses that VEGF-2 binds to tyrosine kinase receptors on the surface of target cells to activate endothelial cell growth." (ANH1 at 3.30.) This statement falsely attributes the teachings of Alitalo et al. to the inventors of the opposed

application. The opposed application contains no teaching whatsoever of the identity of VEGF2 receptors, but only speculation that there are such receptors. More than a year later, when HGS filed its second series of applications on the 419 amino acid VEGF2, HGS still had failed to report the identity of any VEGF2 receptor. (See Documents D44-D46.)

J. MISCELLANEOUS SPECIFIC COMMENTS TO EVIDENCE-IN-ANSWER.

4.104 In this section I try to address any remaining parts of the HGS declarations that appear to relate to issues of fair basis and sufficiency.

J1. AJM1 4.61-4.68

4.105 In paragraphs 4.61-4.68 Dr. Mattick spends about two pages attempting to rebut my explanation that the opposed application fails to teach or exemplify any *active* fragments, analogs, or derivatives of VEGF-2, or any such fragments, analogs, or derivatives with *inhibitory* activity.

4.106 Dr. Mattick first cites to Example 2 as allegedly describing "a fragment." (AJM1 4.63) Even if one fragment is described there, the application provides no evidence or indication that it is "active" or is an "inhibitor". Moreover, as I explain in my first declaration, the description of this example is defective. (See OPR1 at 2.7.20 and 6.6.)

4.107 He also cites an excerpt from page 5 of the opposed application. (AJM1 4.63.) As I explain in my first declaration, this excerpt is nothing more than the inventors attempting to characterize features of the complete VEGF2 molecule - there is no teaching there of fragments. (OPR1 at 3.4.2.) Moreover, even if these were fragments, there is again no teaching or evidence of activity or inhibitory properties.

4.108 Dr. Mattick then launches into a discussion of the experimentation that he could have done to make fragments and then test them for activity or inhibitory properties. This discussion of what Dr. Mattick might have been able to do "to identify" such

molecules only proves my original point that the application itself fails to teach them. His explanation of a research plan for arriving at active fragments, analogs, or derivatives, or inhibitory ones, would be unnecessary if the application had described any active fragments to which he could refer.

J2. AJM1 4.81-4.83

- 4.109 In paragraphs 4.10-4.10.6 of my first declaration I explained that claims in the opposed application defining polypeptides by the ability of antibodies to bind VEGF2 lack any basis in the application. For example, I explained that the application gives no indication that the applicants even intended to define an invention in this manner. (OPR1 4.10.1) Dr. Mattick says he disagrees, but for support, he says that certain pages of the application "provide a variety of suggested uses for which the defined fragments may be used." (AJM1 4.81) Dr. Mattick also urges that he could have made antibodies to the VEGF2 taught in the opposed application. (AJM1 4.82-4.83) He misses the point. Irrespective of whether there would be a use for the polypeptides, the application itself is not directed to such polypeptides. Rather, they appear to be afterthoughts, added to the application in an attempt to cover subject matter invented after the opposed application was filed, such as "full length" VEGF2 on which HGS filed a second application much later, and biologically active VEGF-C polypeptides that were invented by other scientists. (See OPR1 at 4.10-4.10.6.)

J3. AJG1 6.1-6.2

- 4.110 Dr. Gamble credits HGS with succeeding in identifying a VEGF2 gene and polypeptide sequence. (AJG1 6.1) This is inaccurate, in that the proposed application taught an incomplete sequence that cannot be expressed and secreted. When HGS felt that they had identified the complete VEGF2 gene, they filed a second series of VEGF2 patent applications. See discussion in OPR1 at 1.5.1-1.5.1.2 and Documents D44-D46.
- 4.111 Dr. Gamble says that she was aware that the cysteine residues enable the PDGF/VEGF family of proteins to form dimers. (AJG1 6.2) The published evidence

that I have seen suggests that fully processed VEGF-C is different from other members of the family in that cysteines are not involved in forming cysteine-linked dimers. (See Document D71 at p. 3907.)

J4. AJG1 7.15

- 4.112 Dr. Gamble alleges that "The patent specification clearly identifies that VEGF-2 has angiogenic activities, and describes in vitro angiogenic assays of VEGF-2, which could be routinely used." I disagree. There is no description of in vitro angiogenic assays in the patent application. And, to the extent the patent specification "clearly identifies" angiogenic activities, it is only by assertion, unsupported by evidence. In this manner, the patent application also "clearly identifies" many other "activities" such as "to induce the growth of damaged bone, periodontium, or ligament tissues" or to promote the formation of cementum with collagen fiber ingrowths. (See opposed application at p. 17.)

J5. ANH1 3.4

- 4.113 Dr. Hayward declared that "the term VEGF-2 conveys to me the idea of not just the sequences presented in the patent specification, but a family of related sequences. Once a protein has been identified any given sequence can be tested to determine whether any amino acid changes affect the structural and or functional characteristics of that protein." Assuming Dr. Hayward's statements are true in a general sense, they do not apply to VEGF2 taught in the opposed patent application. One cannot test to determine whether amino acid changes affect the structural or functional characteristics of VEGF2 taught in the patent application, because the application does not demonstrate a VEGF2 function, and because VEGF2 taught in the patent application is not expressed and secreted as the application taught it could be.

J6. ANH1 3.37-3.37.5

- 4.114 Dr. Hayward Declared as follows:

3.37 Associate Professor Rogers has commented that fragments of polypeptides have no practical utility whatsoever (see for example paragraph 4.10.2,

Associate Professor Rogers' Statutory Declaration).

Clearly this is not the case. As asserted in the patent specification, fragments of polypeptides can be used to make antibodies, which are useful both experimentally and therapeutically. In addition, active fragments of polypeptides are often used in therapy as antagonists since they can compete with the full length version but may lack full biological activity. Further, such polypeptide fragments could also be used as agonists that might mimic some of the biological activities of the full-length protein. Although the skilled person would be aware of this in any case, I note that the specification discloses the following:

(Dr. Hayward then continues with a discussion of the alleged teachings in the opposed application.)

4.115 Dr. Hayward has misstated what I said in OPR 4.10.2. Paragraph 4.10.2 made no sweeping statements whatsoever applicable to the utility of fragments of all polypeptides. In fact, it made no statement whatsoever about fragments of VEGF2 per se. In that paragraph, I explained that claims 16-27, 40-50, and 57-61 contained no limitations relating to biological activity, and that the specification of the opposed application failed to provide an activity commensurate with the genus being claimed. As I had explained in 4.10.2 and elsewhere in OPR1, the literal scope of those claims encompasses more than just fragments of VEGF2 that might have utility.

4.116 In addition to misunderstanding 4.10.2, Dr. Hayward expresses ideas that require comment.

4.117 For example, he says that fragments of VEGF2 can be used to make antibodies which are useful therapeutically. Since the application fails to demonstrate any biological effect of VEGF2, it is purely speculative to say that antibodies to VEGF2 could be

therapeutic. If someone develops such a therapy, it would owe nothing to the teachings in the opposed application.

- 4.118 Dr. Hayward also declares that VEGF2 antibodies can be used to measure elevated levels of VEGF2 in individuals, and speculates that such levels may be associated with cancer. Again, there is no evidence supporting this speculation in the patent application. If someone discovers such an association and develops a working diagnostic, that development would be due to independent research, and not to the teachings of the patent application. The VEGF2 taught in the patent application cannot be expressed or secreted by cells, as demonstrated by Dr. Alitalo. Thus, the notion of elevated levels of the VEGF2 *taught in the opposed application* has thus been refuted.
- 4.119 Dr. Hayward says fragments are often used in therapy as antagonists since they can compete with the full length version but may lack full biological activity. Again, this is merely speculative, since the patent application fails to demonstrate that the full length VEGF2 has any biological function. In fact, the Alitalo declarations persuasively demonstrate that cells cannot even express and secrete full length VEGF2, as taught in the opposed application, so the notion that there is "the full length version" that needs antagonizing lacks credibility.
- 4.120 Dr. Hayward says some fragments may be used as agonists because they "might mimic some of the biological activities of the full-length protein." As I have stated previously, the whole notion of biological activity or activities of full length VEGF2, taught in the application, is speculative. The notion that fragments could have been made and tested for activities that have not even been demonstrated for full length VEGF2 is even more speculative. If such fragments were found, it would be through the efforts of further research, and not be attributable to the teachings in the application.
- 4.121 Dr. Hayward also declares that the application "clearly demonstrates" that VEGF-2 is expressed at higher levels in cells derived from malignant tumors. I addressed the

apparent errors in the relevant HGS experiment in paragraphs 4.50-4.52, which I repeat by reference.

J7. ANH1 4.10

4.122 Dr. Hayward declared that the process of determining which parts of a polypeptide molecule are required for activity was routine by 1994. If this were true, it pre-supposes at least that the activity of the polypeptide was known to begin with. The experimentation that Dr. Hayward is describing could only have been performed after the extensive experimentation that would have been required to successfully express and secrete VEGF2, and the additional experimentation that would have been required to identify its activity (if any), *and* the additional experimentation to make the mutant forms of VEGF2. This experimentation is extensive and unpredictable, and should not be credited to the opposed application, which taught only an incomplete DNA/protein sequence with no proven activity.

4.123 Dr. Hayward declares that the specification highlights eight cysteines and a 14 amino acid signature motif thought to be involved in VEGF-2 function. The specification identifies these areas as a feature shared with the prior art, but provides little guidance otherwise.

J8. ANH1 4.15

4.124 In paragraph 5.7.1 of my first declaration I explained that the opposed application does not indicate an intent to claim a genus of polypeptides that bind an antibody that binds VEGF-2. Dr. Hayward says he finds such an intention at page 23, lines 5-14. (ANH1 at 4.15.) I have reviewed the application again but disagree with Dr. Hayward. Pages 22-24 relate to alleged methods of making and using antibodies, as Dr. Hayward later alleges himself at ANH1 4.16. Page 23 does not indicate to the reader an intention to define a genus of VEGF2 polypeptides.

LACK OF CLARITY

5.1 In my first declaration I explained that claims 51 and 54 and claims dependent therefrom are confusing in that claim 51 seems to require administration of a polypeptide, but dependent claim 54 seems to say that administration of the polypeptide encompasses the act of administering DNA, an activity that does not involve administration of any polypeptide whatsoever. (OPR1 6.8.2) Dr. Mattick confirms my analysis that these claims suffer from this ambiguity by reading them to permit the limitation "administration . . . of the polypeptide" without administering any polypeptide. (AJM1 at 4.109 - 4.112.)

5.2 Indefiniteness of "fragment, analogue, or derivative" claims.

5.2.1 The declarations provided by HGS provide interpretations of "fragment, analog, or derivative" language that are intended to save the claims from encompassing the prior art. However, those claim interpretations, if adopted, raise substantial issues of vagueness which I explain above in paragraphs 3.18-3.25.4, and repeat hear by reference. Even if the standard that they proposed were understandable, it would result in the scope of the claims changing with time, as new genes are discovered.

5.2.2 Dr. Gamble offered the following interpretation of "fragment, analogue, or derivative" in her declaration:

Reference is made on page 9, line 14 to page 10, line 5 of the specification to the meaning of the terms "fragment", "derivative" and "analog". When I read these passages I understood HGS to be saying that a fragment, derivative or analogue is a polypeptide that retains essentially the same biological function or activity as VEGF-2. (See AJG1 7.7 and 7.8.)

5.2.3 I agree with Dr. Gamble that there is some support at page 9 of the opposed application for this interpretation. However, I also observe that claim 56 is directed to a fragment, analogue, or derivative having an inhibitory activity. Dr. Mattick reads other portions of the application as suggesting that VEGF2

fragments can have VEGF2 inhibitory activity. (See AJM1 4.23.) These claim interpretations are irreconcilable.

5.2.4 Dr. Gamble also offers the following additional guidance about the definition of fragment, analogue, or derivative:

While I acknowledge this basic requirement I am conscious of the fact that before something can be an analogue, fragment or a derivative of a protein it needs to share sufficient identity with that protein to make it resemble that protein or at least part thereof. In my opinion both of these requirements must be satisfied before a sequence of amino acids can truly be called an analogue, fragment or a derivative of VEGF-2. (AJG1 at 7.7)

5.2.5 As I explain in my original declaration and also above, neither the application nor conventional scientific usage clarifies in any meaningful way what "sufficient identity . . . to make it resemble" means. (See OPR1 at 4.6.3; see above at 3.23-3.24.) Even if the concept were understandable, the boundaries are not.

5.3 Indefiniteness of "VEGF2 activity."

As I explained in my first declaration, the opposed application contains no explicit definition of VEGF2 activity (OPR1 at 2.3.1 - 2.3.2.3), but suggests many in vivo or in vitro uses for VEGF2 (all unsupported by evidence). (OPR1 at 2.3.3.) I explained in OPR1 that "VEGF2 activity" and related terms were indefinite. (See OPR1 at 6.5-6.5.1, 2.3-2.3.5, and 4.6-4.8.) HGS's declarations cast still further uncertainty on the meaning of VEGF2 activity, because they are ambiguous about whether "VEGF2 activity" means a single parameter or multiple parameters. If a polypeptide must have "all" of these biological activities, it would be impossible to ever complete the tests to determine them. If "one or more" of these activities is sufficient for "VEGF2

activity", then prior art polypeptides have VEGF2 activity. (See OPR1 at 2.3.) If it is not necessary for the polypeptide to retain all of the supposed VEGF2 in vivo and in vitro properties, it is unclear how many such properties can be "lost" before the polypeptide is no longer considered to have VEGF2 activity.

5.3.1 Dr. Gamble declares that she immediately understands biological function or activity "to include at least in vivo and/or in vitro activity." (AJG1 at 7.8)

The implication of this statement is that she thinks every use mentioned in the patent application, from culturing vascular endothelial cells, providing cancer therapy, promoting bone or periodontium or ligament growth, etc. is VEGF2 activity. It is still ambiguous whether each alone is VEGF2 activity or whether, together, they comprise VEGF2 activity.

5.3.2 Other parts of Dr. Gamble's declaration suggest that a single biological function is sufficient for "VEGF2 activity." For example, in paragraphs 7.9 and 7.10, and again in paragraphs 7.15-7.18, she seems to be suggesting that testing for angiogenic activity alone is a sufficient test for VEGF2 activity.

5.3.3 Still other parts of Dr. Gamble's declaration suggest that a single biological function is NOT sufficient for "VEGF2 activity." For example, in AJG1 7.11, Dr. Gamble says that whether or not a polypeptide promotes *endothelial cell growth* is a means for distinguishing a polypeptide that has VEGF2 activity from a PDGFa or PDGFb polypeptide, which she says do not promote growth of endothelial cells. Here, she seems to be saying that all VEGF2 polypeptides have at least endothelial cell growth activity (because that is how they can be distinguished from PDGF polypeptides). This endothelial growth activity must be in addition to the "angiogenic" activity she says she could have easily screened for (in AJG1 7.9-7.10 and 7.15-7.18), because Dr. Gamble teaches that PDGF polypeptides also have angiogenic activity. (See Litwin, Gamble, and Vadas, Annexure GBC-10 of the HGS evidence, at page 105 (PDGF "has roles in wound healing and angiogenesis").)

5.3.4 Dr. Hayward says that VEGF2 activity means "one or more" of a list of about seven activities that he selected from the patent application. (See ANH1 3.6) His list explicitly *omitted* many other functions also taught in the patent application, such as growth of damaged bone, periodontium, or ligament tissue as stated at page 17 of the opposed application. It is not clear whether Dr. Hayward now classifies one or more of these other functions as VEGF2 activities. (At paragraph 4.4, Dr. Hayward makes generic reference to all of the activities recited at pages 4 and 16-18 of the application.) Dr. Hayward also is of the opinion that whether the specification teaches a unique defining activity for VEGF2 is irrelevant. (ANH1 at 4.3.)

5.3.5 Thus, even when HGS's declarants are trying to explain the alleged simplicity of understanding and screening for VEGF2 activity, they create more questions than answers. If VEGF2 means "angiogenic activity" then why did the application teach that VEGF2 did so many other things, and how does "VEGF2 activity" distinguish the angiogenic PDGF and VEGF polypeptides of the prior art? If "VEGF2 activity" means the combination of "endothelial growth activity" AND "angiogenesis activity" (per Dr. Gamble, to exclude PDGF from the claims), then why does Dr. Gamble suggest in other paragraphs of her declaration that the only testing she would have needed to do was testing for "angiogenic activity"? And how does this definition of "VEGF2 activity" exclude prior art VEGF polypeptides, which promote endothelial cell growth and angiogenesis? If the combination of "angiogenic activity" and "endothelial growth activity" are the two functions that HGS says are the critical ones for defining "VEGF2 activity", then why does the application identify so many other functions, and why do the experts broadly say that "VEGF2 activity is "in vitro and/or in vivo" activity? And why (except perhaps for hindsight) did the HGS declarants select angiogenic activity and/or endothelial cell growth activity as the two important activities, to the exclusion of all of the other functions mentioned in the application? If a protein induces the growth of damaged bone, periodontium, or ligament tissue as stated at page 17 of the opposed application, does that protein have VEGF2

activity? Does the answer depend on whether it also promotes angiogenesis and endothelial cell growth? For all of these reasons, I find that the declarations of Dr. Gamble and others only confuse further the meaning of "VEGF2 activity."

- 5.3.6 HGS's continued assertion that VEGF2 activity includes antigenic activity (the ability to cause antibody production) raises still more questions. (See paragraphs 3.32-3.35, repeated here by reference.)

5.4 Indefiniteness of "polypeptide binds an antibody which binds to VEGF-2"

- 5.4.1 At least claims 16-22 and 40-50 of the opposed application recite, or depend from claims that recite, the limitation "polypeptide binds an antibody which binds to VEGF-2" or some close variation thereof.

- 5.4.2 HGS's declarants ask the Patent Office to believe that antibody cross-reactivity is simply too unpredictable to draw any conclusions from looking at protein sequences. Exemplary excerpts from the HGS evidence follows:

Associate Professor Rogers appears to suggest (see, for example paragraph 2.7.16) that antibodies that bind to regions of VEGF-2 that are conserved with other PDGF/VEGF family members might be cross-reactive. Associate Professor Rogers refers to a number of prior art disclosures of anti-VEGF or anti-PDGF antibodies. Simply because two sequences share some homology does not necessarily imply that any antibody produced against one molecule would necessarily be cross-reactive against the other. In my opinion no conclusion can be made as to whether sequences sharing some homology will generate antibodies that are cross reactive. (AJG1 7.21)

The fact that there is some sequence homology between VEGF-2 and VEGF and other proteins does not mean that there is a high probability that antibodies to VEGF-2 will cross react with VEGF or those other proteins. Antibodies generally have exquisite specificity and will only cross react with closely related proteins. I do not believe that any conclusion can be drawn about cross-reactive antibodies at a theoretical or practical level.

(AJM1 at 4.33)

5.4.3 If the Patent Office accepts the premise of HGS's experts, then I believe it should also find that all of the relevant claims which attempt to define subject matter with an antibody binding limitation are indefinite. If no predictions can be made, then HGS is saying that the public is required to physically screen a polypeptide with every antibody that anyone could ever generate against VEGF-2, in order to determine whether the polypeptide falls within a claim. That is clearly an impossible task. The boundaries of the claims are still further obscured because the cutoff level of binding is unspecified.

5.4.4 When criticizing the Alitalo declaration, HGS's declarants ask the Patent Office to believe that the results of an antibody binding experiment can be manipulated to achieve any desired result, by varying such parameters as antibody chosen (because antibodies have different binding affinities); selection of polyclonal versus monoclonal antibodies; the amount of antibodies used; and the lack of established controls. (See, e.g., ANH1 at 5.7.) If the Patent Office accepts HGS's position on this issue, then logically, it must also conclude that all of the claims that define a genus of polypeptides by whether they bind an antibody that binds VEGF2 are unclear. The essence of what HGS is saying is that whether an antibody binds to a VEGF2 polypeptide can be manipulated to achieve a desired result, unless a number of parameters are carefully defined. None of those parameters are defined in the opposed application or the claims at issue. In fact, the entire notion of VEGF2

antibody binding is theoretical in the opposed application, since no antibodies are taught. If antibody binding is subject to all of the variables and manipulations identified by HGS, then the metes and bounds of the claims are also unpredictably variable and subject to manipulation, and cannot be considered clear.

5.5 Indefiniteness of "hybridisation" language in the claims.

5.5.1 I explained that hybridization language in the claims was confusing in my original declaration. (See, e.g., OPR1 at 6.7 - 6.7.2.)

5.5.2 Dr. Hayward discusses hybridization claim language at ANH1 3.9-3.12. He says that, "When I read the word 'hybridise' in those claims I understand it to mean that the hybridisation reaction should be conducted under suitably stringent conditions such that only VEGF-2 polynucleotide sequences would bind either nucleotide sequence shown in the sequence listing (SEQ ID No. 1) or the cDNA deposited in the ATCC deposit identified in the patent specification or fragments thereof." Needless to say, Dr. Hayward's definition is totally circular. He says he would define the VEGF2 subject matter of the claims as encompassing VEGF2 subject matter.

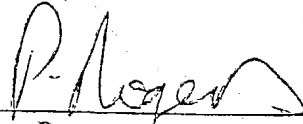
5.5.3 To the extent that Dr. Hayward believes that "VEGF2" can include variants of the precise VEGF2 sequence taught in the application, such as non-human "orthologs" (suggested in ANH1 at 3.3), the application gives no guidance as to how dissimilar such sequences are or what hybridization conditions would be appropriate for distinguishing them, so the metes and bounds of the claims cannot be ascertained.

AND I MAKE this solemn declaration by virtue of the Statutory Declarations Act 1959, and subject to the penalties provided by that Act for the making of false statements in statutory

declarations, conscientiously believing the statements contained in this declaration to be true in every particular.

DECLARED at Melbourne, Victoria

This 12th day of November, 2001



Peter Adrian Walton Rogers

Before me:



(Signature of Witness)

Medical Practitioner

AUSTRALIA

Patents Act 1990

IN THE MATTER OF Australian Patent
Application Serial No. 696764 by Human
Genome Sciences, Inc.

-and-

IN THE MATTER OF Opposition thereto by
Ludwig Institute for Cancer Research

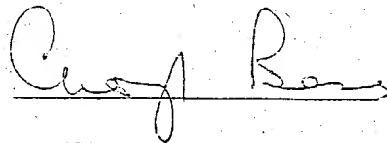
THIS IS Exhibit PAWR-1

referred to in the Statutory Declaration

of Peter Adrian Walton Rogers

made before me.

DATED this 12th Day of November, 2001

A handwritten signature in cursive script, appearing to read 'Craig Ross', written over a horizontal line.

(Signature of Witness)

Medical Practitioner

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(54) Title: HUMAN VASCULAR ENDOTHELIAL GROWTH FACTOR 2			
(57) Abstract			
<p>Disclosed is a human VEGF2 polypeptide and DNA (RNA) encoding such VEGF2 polypeptides. Also provided is a procedure for producing such polypeptide by recombinant techniques and antibodies and antagonist against such polypeptide. Also disclosed is a method of using such polypeptide for stimulating wound healing and for vascular tissue repair. Also provided are methods of using the antagonists to inhibit tumor growth, inflammation and to treat diabetic retinopathy, rheumatoid arthritis and psoriasis. Diagnostic methods for detecting mutations in the VEGF2 coding sequence and alterations in the concentration of VEGF2 protein in a sample derived from a host are also disclosed.</p>			

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. An isolated polynucleotide comprising a member selected from the group consisting of:
 - a) a polynucleotide encoding the full length polypeptide as set forth in SEQ ID NO: 2;
 - b) a polynucleotide encoding the mature protein portion of SEQ ID NO:2;
 - c) a polynucleotide encoding the proprotein portion of SEQ ID NO: 2;
 - d) a polynucleotide encoding the human VEGF-2 polypeptide encoded by the cDNA in ATCC Deposit No. 97149;
 - e) a polynucleotide comprising the nucleotide sequence encoding a polypeptide comprising amino acid residues -46 to 373 of SEQ ID NO: 2;
 - f) a polynucleotide comprising the nucleotide sequence encoding a polypeptide comprising amino acid residues -23 to 373 of SEQ ID NO: 2;
 - g) a polynucleotide comprising the nucleotide sequence encoding a polypeptide comprising amino acids 1 to 373 of SEQ ID NO: 2;
 - h) a polynucleotide comprising the nucleotide sequence encoding a portion of the mature VEGF-2 polypeptide comprising amino acids 24 to 373 of SEQ ID NO: 2;
 - i) a polynucleotide comprising the nucleotide sequence encoding a polypeptide comprising amino acids -46 to 24 of SEQ ID NO: 2;
 - j) a polynucleotide comprising the nucleotide sequence encoding a polypeptide comprising amino acids -23 to 24 of SEQ ID NO: 2;
 - k) a polynucleotide comprising the nucleotide sequence encoding a polypeptide comprising amino acids 1 to 24 of SEQ ID NO: 2;
 - l) a polynucleotide fragment of the polynucleotide according to any one of a) to d) with the proviso that said polynucleotide fragment comprises at least 30 contiguous nucleotides of the polynucleotide of i), j) or k);
 - m) a polynucleotide fragment which hybridises to at least 30 contiguous nucleotides of the polynucleotide encoding amino acids -46 to 24 of SEQ ID NO: 2 under the following conditions: hybridisation in 0.5 M sodium peroxide



NaPO₄, 7% sodium dodecyl sulfate (SDS) at 65°C and washing with 0.5 x SSC, 0.1% SDS at 60°C or equivalent hybridisation stringency;

- n) a polynucleotide comprising the complementary form of the polynucleotide according to any one of a) to m).
-
2. An isolated polynucleotide according to claim 1 wherein the polynucleotide encodes the full length polypeptide as set forth in SEQ ID NO: 2.
 3. An isolated polynucleotide according to claim 1 wherein the polynucleotide encodes the mature protein portion of SEQ ID NO:2.
 4. An isolated polynucleotide according to claim 1 wherein the polynucleotide encodes the proprotein portion of SEQ ID NO: 2.
 5. An isolated polynucleotide according to claim 1 wherein the polynucleotide encodes the human VEGF-2 polypeptide encoded by the cDNA in ATCC Deposit No. 97149.
 6. An isolated polynucleotide according to claim 1 wherein the polynucleotide encodes a polypeptide comprising amino acids -46 to 373 of SEQ ID NO: 2.
 7. An isolated polynucleotide according to claim 1 wherein the polynucleotide encodes a polypeptide comprising amino acids -23 to 373 of SEQ ID NO: 2.
 8. An isolated polynucleotide according to claim 1 wherein the polynucleotide encodes a polypeptide comprising amino acids 1 to 373 of SEQ ID NO: 2.
 9. An isolated polynucleotide according to claim 1 wherein the polynucleotide encodes a portion of the mature VEGF-2 polypeptide comprising amino acids 24 to 373 of SEQ ID NO: 2.
 10. An isolated polynucleotide according to claim 1 wherein the polynucleotide encodes



SEQ ID NO: 2;

- d) a polypeptide comprising the amino acid sequence of the mature polypeptide encoded by the cDNA contained in ATCC Deposit No. 97149;
 - e) a polypeptide comprising amino acids -46 to 373 of SEQ ID NO: 2;
 - f) a polypeptide comprising amino acids -23 to 373 of SEQ ID NO: 2;
 - g) a polypeptide comprising amino acids 1 to 373 of SEQ ID NO: 2;
 - h) a portion of the mature VEGF-2 polypeptide comprising amino acids 24 to 373 of SEQ ID NO:2;
 - i) a polypeptide comprising amino acids -46 to 24 of SEQ ID NO: 2;
 - j) a polypeptide comprising amino acids -23 to 24 of SEQ ID NO: 2;
 - k) a polypeptide comprising amino acids 1 to 24 of SEQ ID NO: 2;
 - l) a polypeptide comprising an active fragment of the VEGF2 polypeptides according to any one of a) to d) with the proviso that part of said polypeptide fragment is encoded by at least 30 contiguous nucleotides of the polynucleotide encoding the polypeptide of any one of i), j) or k);
 - m) a polypeptide fragment comprising an amino acid sequence encoded by a polynucleotide sequence which hybridises to at least 30 contiguous nucleotides of the polynucleotide encoding any one of the polypeptides of i), j) or k) under the following conditions: hybridisation in 0.5 M sodium peroxide NaPO_4 , 7% sodium dodecyl sulfate (SDS) at 65°C and washing with 0.5 x SSC, 0.1% SDS at 60°C or equivalent hybridisation stringency.
17. An isolated polypeptide according to Claim 15 comprising the amino acid sequence of the full length polypeptide of SEQ ID NO:2.
18. An isolated polypeptide according to Claim 16 comprising the amino acid sequence of the mature portion of SEQ ID NO: 2.
19. An isolated polypeptide according to Claim 16 comprising a polypeptide comprising the amino acid sequence of the proprotein portion of SEQ ID NO: 2.



20. An isolated polypeptide according to Claim 16 comprising the amino acid sequence of the mature VEGF-2 polypeptide encoded by the cDNA contained in ATCC Deposit No. 97149.
21. An isolated polypeptide according to Claim 16 comprising amino acids -46 to 373 of SEQ ID NO: 2.
22. An isolated polypeptide according Claim 16 comprising amino acids -23 to 373 of SEQ ID NO: 2.
23. An isolated polypeptide according to Claim 16 comprising amino acids 1 to 373 of SEQ ID NO: 2.
24. An isolated portion of the mature VEGF-2 polypeptide according to Claim 16 comprising amino acids 24 to 373 of SEQ ID NO: 2.
25. An isolated polypeptide according to Claim 16 comprising amino acids -46 to 24 of SEQ ID NO: 2.
26. An isolated polypeptide according to Claim 16 comprising amino acids -23 to 24 of SEQ ID NO: 2.
27. An isolated polypeptide according to Claim 16 comprising amino acids 1 to 24 of SEQ ID NO: 2.
28. An isolated polypeptide according to Claim 16 comprising a fragment of any one of the polypeptides of Claims 16 to 20 with the proviso that part of said polypeptide fragment is encoded by at least 30 contiguous nucleotides of the polynucleotide encoding the polypeptide of any one of Claims 25 to 27.
29. An isolated polypeptide according to Claim 16 comprising an amino acid sequence



encoded by a polynucleotide sequence which hybridises to at least 30 contiguous nucleotides of the polynucleotide encoding any one of the polypeptides of Claims 25 to 27 under the following conditions: hybridisation in 0.5 M sodium peroxide NaPO_4 , 7% sodium dodecyl sulfate (SDS) at 65°C and washing with 0.5 x SSC, 0.1% SDS at 60°C or equivalent hybridisation stringency.

30. An isolated polypeptide according to any one of Claims 16 to 29 further comprising a heterologous polypeptide.
31. An isolated polypeptide according to any one of Claims 16 to 30 further comprising a homodimer.
32. An isolated polypeptide according to any one of Claims 16 to 31 wherein the polypeptide is glycosylated.
33. A composition comprising the polypeptide according to any one of Claims 16 to 32 or 40 and one or more pharmaceutically acceptable carriers and /or diluents.
34. A vector comprising the polynucleotide according to any one of Claims 1 to 15.
35. A recombinant vector comprising the polynucleotide according to any one of Claims 1-15 operatively associated with a regulatory sequence that controls gene expression.
36. A host cell comprising the polynucleotide according to any one of Claims 1-15 operably associated with a heterologous regulatory sequence or a vector comprising same.
37. The polynucleotide sequence according to any one of Claims 1-15 further comprising a heterologous polynucleotide.
38. The polynucleotide sequence of Claim 37 further comprising a polynucleotide which



encodes a heterologous polypeptide.

39. A method for producing a VEGF-2 polypeptide at least comprising the step of culturing the genetically engineered host cell of Claim 36 for a time and under conditions suitable for the expression of the polypeptide encoded by said polynucleotide to occur.
40. A polypeptide produced by the method of Claim 39.
41. A composition comprising the polynucleotide according to any one of Claims 1-15, 37, or 38 and one or more pharmaceutically acceptable carriers and/or diluents.
42. Use of the polynucleotide according to any one of Claims 1 to 15, 37 or 38 or the polypeptide according to any one of Claims 16 to 32 or 40 in the preparation of a medicament for the treatment of a patient having need of human VEGF-2 polypeptide.
43. An antibody which is capable of binding to the polypeptide according to any one of Claims 16 to 29 with the proviso that the antibody is not capable of binding to a polypeptide consisting of amino acid residues 24 to 373 of SEQ ID NO: 2 or a fragment thereof.
44. An antisense construct capable of binding to the polynucleotide according to any one of Claims 1-15 or a complementary form thereof with the proviso that the antisense construct is not capable of binding to a polynucleotide sequence encoding amino acids 24 to 373 of SEQ ID NO: 2 or a fragment thereof.
45. A method of stimulating proliferation of endothelial cells in a patient comprising administering to the patient the polypeptide according to any one of Claims 16 to 32 or 40 for a time and under conditions sufficient for the proliferation of endothelial cells to occur.



- 63 -

to the Figures and/or Examples.

58. The composition of Claim 33 or 41 substantially as hereinbefore described with reference to the Figures and/or Examples.

DATED this EIGHTH day of NOVEMBER, 1999

Human Genome Sciences, Inc.

DAVIES COLLISON CAVE

Patent Attorneys for the Applicant



AUSTRALIA

Patents Act 1990

IN THE MATTER OF Australian Patent
Application Serial No. 696764 by Human
Genome Sciences, Inc.

-and-

IN THE MATTER OF Opposition thereto by
Ludwig Institute for Cancer Research

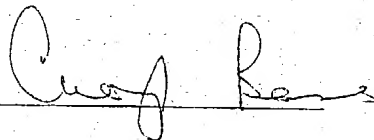
THIS IS Exhibit PAWR-2

referred to in the Statutory Declaration

of Peter Adrian Walton Rogers

made before me

DATED this 12th Day of November, 2001

A handwritten signature in cursive script, appearing to read 'Craig Rose', written over a horizontal line.

(Signature of Witness)

Medical Practitioner

(12) PATENT
(19) AUSTRALIAN PATENT OFFICE

(11) Application No. AU 199653665 B2
(10) Patent No. 726486

(54) Title
Human tumor necrosis factor delta and epsilon

(51)⁷ International Patent Classification(s)
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C07H 021/04 C12N 015/09
C07K 001/00 C12N 015/63
C07K 014/00

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(56) Related Art
US 5487984
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IN

(51) International Patent Classification γ : C07H 21/02, 21/04, C07K 1/00, 14/00, C12N 5/00, 15/09, 15/63 SEARCH QUALITY ASSURANCE	A1	(11) International Publication Number: WO 97/33902 (43) International Publication Date: 18 September 1997 (18.09.97)
(21) International Application Number: PCT/US96/03774 (22) International Filing Date: 14 March 1996 (14.03.96) (71) Applicant (for all designated States except US): HUMAN GENOME SCIENCES, INC. [US/US]; 9410 Key West Avenue, Rockville, MD 20850-3338 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): NI, Jian [CN/US]; 5502 Manorfield Road, Rockville, MD 20853 (US). YU, Guo-Liang [CN/US]; 13524 Straw Bale Lane, Darnestown, MD 20878 (US). GENTZ, Reiner, L. [DE/US]; 13404 Fairland Park Drive, Silver Spring, MD 20904 (US)., Patrick J. Dillon (74) Agents: HERRON, Charles, J.; Carella, Byrne, Bain, Gilfillan, Cecchi, Stewart & Olstein, 6 Becker Farm Road, Roseland, NJ 07068 (US) et al.		(81) Designated States: AM, AU, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KG, KP, KR, KZ, LT, LV, MD, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published With international search report. 
(54) Title: HUMAN TUMOR NECROSIS FACTOR DELTA AND EPSILON		
(57) Abstract		
<p>The invention relates to human TNF delta and TNF epsilon polypeptides, polynucleotides encoding the polypeptides, methods for producing the polypeptides, in particular by expressing the polynucleotides, and agonists and antagonists of the polypeptides. The invention further relates to methods for utilizing such polynucleotides, polypeptides, agonists and antagonists for applications, which relate, in part, to research, diagnostic and clinical arts.</p>		

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS

1. An isolated polynucleotide comprising a polynucleotide sequence selected from the group consisting of:-
 - (a) a polynucleotide sequence encoding a polypeptide comprising an amino acid sequence as set forth in SEQ ID NO:2;
 - (b) a polynucleotide sequence encoding a polypeptide comprising an amino acid sequence as set forth in SEQ ID NO:4;
 - (c) a polynucleotide sequence encoding a polypeptide comprising amino acid 39 to amino acid 233 of SEQ ID NO:2;
 - (d) a polynucleotide sequence having at least 70% identity to the polynucleotide sequence of (a), (b) or (c) and encoding a polypeptide having TNF-delta and/or TNF-epsilon activity;
 - (e) a polynucleotide sequence comprising at least 30 contiguous bases of the polynucleotide sequence of (a), (b), (c) or (d) and encoding a polypeptide having TNF-delta and/or TNF-epsilon activity;
 - (f) a polynucleotide sequence comprising at least 50 contiguous bases of the polynucleotide sequence of (a), (b), (c) or (d) and encoding a polypeptide having TNF-delta and/or TNF-epsilon activity;
 - (g) a polynucleotide sequence comprising a fragment of the polynucleotide sequence of (a), (b), (c) or (d), wherein said fragment encodes a polypeptide that retains TNF-delta and/or TNF-epsilon activity;
 - (h) a polynucleotide sequence of (g) which encodes at least 30-50 amino acids of SEQ ID No's 2 or 4; and
 - (i) a polynucleotide sequence which is complementary to the polynucleotide sequence of (a), (b), (c), (d), (e), (f), (g) or (h).
2. The polynucleotide of Claim 1 wherein the polynucleotide is DNA.
3. The polynucleotide of Claim 1 wherein the polynucleotide is RNA.
4. The polynucleotide of Claim 1 wherein the polynucleotide is genomic DNA.
5. The polynucleotide of Claim 2 which encodes a polypeptide comprising the amino acids of SEQ ID NO:2.



6. The polynucleotide of Claim 2 which encodes a polypeptide comprising amino acid 39 to 233 of SEQ ID NO:2.
7. The polynucleotide of Claim 2 which encodes a polypeptide comprising the amino acids of SEQ ID NO:4.
8. The polynucleotide of Claim 2 which encodes a polypeptide comprising the amino acids 1 to 188 of SEQ ID NO:4.
9. An isolated polynucleotide comprising a polynucleotide selected from the group consisting of:-
 - (a) a polynucleotide which encodes a mature polypeptide having the amino acid sequence expressed by the human cDNA contained in ATCC Deposit No. 97377;
 - (b) a polynucleotide which encodes a mature polypeptide having the amino acid sequence expressed by the human cDNA contained in ATCC Deposit No. 97457;
 - (c) a polynucleotide sequence having at least 70% identity to the polynucleotide sequence of (a) or (b) and encoding a polypeptide having TNF-delta and/or TNF-epsilon activity;
 - (d) a polynucleotide sequence comprising at least 30 contiguous bases of the polynucleotide of (a), (b) or (c) and encoding a polypeptide having TNF-delta and/or TNF-epsilon activity;
 - (e) a polynucleotide sequence comprising at least 50 contiguous bases of the polynucleotide sequence of (a), (b) or (c) and encoding a polypeptide having TNF-delta and/or TNF-epsilon activity;
 - (f) a polynucleotide comprising a fragment of the polynucleotide of (a), (b) or (c), wherein said fragment encodes a polypeptide that retains TNF-delta and/or TNF-epsilon activity;
 - (g) a polynucleotide sequence of (f) which encodes at least 30-50 amino acids of the polypeptide encoded by ATCC Deposit No's 97377 or 97457; and
 - (h) a polynucleotide which is complementary to the polynucleotide of (a), (b), (c), (d), (e), (f) or (g).

10. The polynucleotide of Claim 1 comprising from nucleotide 447 to nucleotide 1717 of SEQ ID NO:1.
11. The polynucleotide of Claim 1 comprising from nucleotide 332 to nucleotide 1717 of SEQ ID NO:1.
12. The polynucleotide of Claim 1 comprising from nucleotide 1 to nucleotide 564 of SEQ ID NO:3.
13. A vector comprising the DNA of Claim 2.
14. A host cell comprising the vector of Claim 13.
15. A process for producing a polypeptide comprising expressing from the host cell of Claim 14 the polypeptide encoded by the DNA in said vector.
16. A process for producing a cell comprising genetically engineering the cell with the vector of Claim 12 to thereby express the polypeptide encoded by the human cDNA contained in the vector.
17. A polypeptide comprising a member selected from the group consisting of:-
 - (a) a polypeptide having an amino acid sequence as set forth in SEQ ID NO:2;
 - (b) a polypeptide having an amino acid sequence as set forth in SEQ ID NO:4;
 - (c) a polypeptide comprising amino acid residues 39 to 233 of SEQ ID NO:2;
 - (d) a polypeptide comprising amino acid residues 1 to 188 of SEQ ID NO:4;
 - (e) a polypeptide having at least a 70% identity to the polypeptide of (a), (b), (c) or (d) and having TNF-delta and/or TNF-epsilon activity;
 - (f) a polypeptide comprising at least 30 contiguous amino acid residues of the polypeptide of (a), (b), (c), (d) or (e) and having TNF-delta and/or TNF-epsilon activity.

18. The polypeptide of Claim 17 wherein the polypeptide comprises amino acid 1 to amino acid 233 of SEQ ID NO:2.
19. The polypeptide of Claim 17 wherein the polypeptide comprises amino acid 39 to amino acid 233 of SEQ ID NO:2.
20. The polypeptide of Claim 17 wherein the polypeptide comprises amino acid 1 to amino acid 188 of SEQ ID NO:4.
21. A compound which inhibits activation of the polypeptide of Claim 17.
22. A method for the treatment of a patient having need of TNF delta comprising administering to the patient a therapeutically effective amount of the polypeptide of Claim 17.
23. A method for the treatment of a patient having need of TNF epsilon comprising administering to the patient a therapeutically effective amount of the polypeptide of Claim 17.
24. A method of Claim 22 wherein said therapeutically effective amount of the polypeptide is administered by providing to the patient DNA encoding said polypeptide and expressing said polypeptide *in vivo*.
25. A method of Claim 23 wherein said therapeutically effective amount of the polypeptide is administered by providing to the patient DNA encoding said polypeptide and expressing said polypeptide *in vivo*.
26. A method for the treatment of a patient having need to inhibit a TNF delta polypeptide comprising administering to the patient a therapeutically effective amount of the compound of Claim 21.
27. A method for the treatment of a patient having need to inhibit a TNF epsilon polypeptide comprising administering to the patient a therapeutically effective amount of the compound of Claim 21.

28. A process for diagnosing a disease or a susceptibility to a disease related to an under-expression of the polypeptide of Claim 17 comprising determining a mutation in a nucleic acid sequence encoding said polypeptide.
29. A diagnosis process comprising analysing for the presence of the polypeptide of claim 17 in a sample derived from a host.
30. A method for identifying compounds which bind to and inhibit activation of the polypeptide of Claim 17 comprising:-
 - contacting a cell expressing on the surface thereof a receptor for the polypeptide, said receptor being associated with a second component capable of providing a detectable signal in response to the binding of a compound to said receptor, with an analytically detectable TNF delta polypeptide and a compound under conditions to permit binding to the receptor; and
 - determining whether the compound binds to and inhibits the receptor by detecting the absence of a signal generated from the interaction of the TNF delta with the receptor.
31. An isolated polynucleotide comprising a polynucleotide sequence having at least 90% identity to a member of the group (a), (b), (c), (d), (e), (f), (g) or (h) in claim 1 and encoding a polypeptide having TNF-delta and/or TNF-epsilon activity.
32. An isolated polynucleotide comprising a polynucleotide sequence having at least 95% identity to a member of the group (a), (b), (c), (d), (e), (f), (g) or (h) in claim 1 and encoding a polypeptide having TNF-delta and/or TNF-epsilon activity.
33. An isolated polynucleotide comprising a polynucleotide sequence encoding a polypeptide with TNF-delta and/or TNF-epsilon activity and which hybridises to the complement of the polynucleotide set forth in SEQ ID NO:1 wherein said hybridisation occurs under conditions comprising hybridisation in a buffer consisting of 7% SDS, 0.5 M NaPO₄ pH 7.4 at 65°C and wash in a solution consisting of 0.5 x SSC, 0.1% SDS at 60°C.
34. An isolated polynucleotide comprising a polynucleotide sequence encoding a polypeptide with TNF-delta and/or TNF-epsilon activity and which hybridises to

the complement of the polynucleotide set forth in SEQ ID NO:3 wherein said hybridisation occurs under conditions comprising hybridisation in a buffer consisting of 7% SDS, 0.5 M NaPO_4 pH 7.4 at 65°C and wash in a solution consisting of 0.5 x SSC, 0.1% SDS at 60°C.

35. The isolated polypeptide of Claim 17 wherein said polypeptide comprises an amino acid sequence having at least 90% identity to a member of said group (a), (b), (c), (d), (e) or (f) and retains TNF-delta and/or TNF-epsilon activity.
36. The isolated polypeptide of Claim 17 wherein said polypeptide comprises an amino acid sequence having at least 95% identity to a member of said group (a), (b), (c), (d), (e) or (f) and retains TNF-delta and/or TNF-epsilon activity.
37. An isolated polynucleotide according to any one of Claims 1 to 12 or a vector according to Claim 13 or a host cell according to Claim 14 or a process according to Claims 15 or 16 or a polypeptide according to any one of Claims 17 to 20 or a compound according to Claim 21 or a method according to any one of Claims 22 to 30 or a polynucleotide according to any one of Claims 31 to 34 or a polypeptide according to Claim 35 or 36 substantially as hereinbefore described with reference to the Figures and/or Examples.

AUSTRALIA

Patents Act 1990

IN THE MATTER OF Australian Patent
Application Serial No. 696764 by Human
Genome Sciences, Inc.

-and-

IN THE MATTER OF Opposition thereto by
Ludwig Institute for Cancer Research

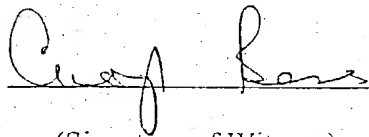
THIS IS Exhibit PAWR-3

referred to in the Statutory Declaration

of Peter Adrian Walton Rogers

made before me

DATED this 12th Day of November, 2001



(Signature of Witness)

Medical Practitioner

(12) PATENT
(19) AUSTRALIAN PATENT OFFICE

(11) Application No. AU 199512547 B2
(10) Patent No. 708972

(54) Title
Tumor necrosis factor-gamma

(51)⁶ International Patent Classification(s)
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A61K 031/70 C12N 015/28
A61K 035/14 C12P 021/06
A61K 045/05 C12Q 001/68

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(56) Related Art
US 4677063

NUCLEIC ACIDS RESEARCH 13(17) 1985 PP.6361-6373

P.N.A.S. 86 1989 PP.10104-10107



<p>(51) International Patent Classification 6 : C07H 17/00, C12P 21/06, C07K 14/00, C12Q 1/68, A61K 31/70, 35/14, 45/05, C12N 5/00, 15/00</p>	<p>A1</p>	<p>(11) International Publication Number: WO 96/14328 (43) International Publication Date: 17 May 1996 (17.05.96)</p>
<p>(21) International Application Number: PCT/US94/12880 (22) International Filing Date: 7 November 1994 (07.11.94) (71) Applicant (for all designated States except US): HUMAN GENOME SCIENCES, INC. [US/US]; 9410 Key West Avenue, Rockville, MD 20850-3338 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): YU, Guo-Liang [CN/US]; 13524 Straw Bale Lane, Darnestown, MD 20878 (US). NI, Jian [CN/US]; Apartment 204, 305 Westside Drive, Gaithersburg, MD 20878 (US). ROSEN, Craig, A. [US/US]; 22400 Rolling Hill Road, Laytonsville, MD 20882 (US). (74) Agents: OLSTEIN, Elliot, M. et al.; Carella, Byrne, Bain, Gilfillan, Cecchi, Stewart & Olstein, 6 Becker Farm Road, Roseland, NJ 07068 (US).</p>		<p>(31) Designated States: AU, CA, CN, JP, KR, NZ, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published With international search report.</p>
<p>(54) Title: TUMOR NECROSIS FACTOR-GAMMA (57) Abstract A human TNF-gamma polypeptide and DNA (RNA) encoding such polypeptide and a procedure for producing such polypeptide by recombinant techniques is disclosed. Also disclosed are methods for utilizing such polypeptide to inhibit cellular growth, for example in a tumor or cancer, for facilitating wound-healing, to provide resistance against infection, induce inflammatory activities, and stimulating the growth of certain cell types to treat diseases, for example restenosis. Also disclosed are diagnostic methods for detecting a mutation in the TNF-gamma nucleic acid sequence or an overexpression of the TNF-gamma polypeptide. Antagonists against such polypeptides and their use as a therapeutic to treat cachexia, septic shock, cerebral malaria, inflammation, arthritis and graft-rejection are also disclosed.</p>		

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. An isolated polynucleotide which encodes a tumor necrosis factor (TNF- γ) polypeptide, wherein said polynucleotide comprises a nucleotide sequence selected from the group consisting of:
 - (a) a nucleotide sequence encoding amino acid residues -25 to 149 of SEQ ID NO:2;
 - (b) a nucleotide sequence encoding the full-length polypeptide encoded by the human cDNA contained in ATCC Deposit No. 75927;
 - (c) a nucleotide sequence encoding amino acid residues 1 to 149 of SEQ ID NO:2;
 - (d) a nucleotide sequence encoding the mature polypeptide encoded by the human cDNA contained in ATCC Deposit No. 75927;
 - (e) a homologue or analogue of any one of (a) to (d), wherein said homologue or analogue is at least 70% identical to any one of (a) to (d) and encodes a peptide or polypeptide having TNF- γ activity;
 - (f) a fragment of any one of (a) to (d), wherein said fragment comprises at least 30 contiguous nucleotides in length derived from any one of (a) to (d);
 - (h) a nucleotide sequence of at least 30 nucleotides in length that is capable of hybridizing to any one of (a) to (e) wherein said nucleotide sequence encodes TNF- γ or is derived from a nucleotide sequence that encodes TNF- γ ; and
 - (i) a nucleotide sequence complementary to any one of (a) to (h).
2. The isolated polynucleotide of claim 1 wherein said nucleotide sequence encodes amino acid residues -25 to 149 of SEQ ID NO:2.
3. The isolated polynucleotide of claim 1 wherein said nucleotide sequence encodes amino acid residues 1 to 149 of SEQ ID NO:2;
4. The isolated polynucleotide of claim 1 wherein said nucleotide sequence encodes the full-length polypeptide encoded by the human cDNA contained in ATCC Deposit



No. 75927.

5. The isolated polynucleotide of claim 1 wherein said nucleotide sequence encodes the mature polypeptide encoded by the human cDNA contained in ATCC Deposit No. 75927.

6. The isolated polynucleotide of claim 1 wherein the percentage identity to a homologue or analogue of any one of (a) to (d) is at least 95%.

7. The isolated polynucleotide of claim 1 wherein the fragment of any one of (a) to (d) comprises at least 50 contiguous nucleotides in length derived from any one of (a) to (d).

8. An isolated polynucleotide which encodes a tumor necrosis factor (TNF- γ) polypeptide, wherein said polynucleotide comprises the nucleotide sequence set forth as SEQ ID NO:1 or at least 30 contiguous nucleotide residues derived therefrom.

9. An isolated polynucleotide which encodes a tumor necrosis factor (TNF- γ) polypeptide, wherein said polynucleotide comprises a nucleotide sequence which is identical to the nucleotide sequence of the human cDNA contained in ATCC Deposit No. 75927 or at least 30 contiguous nucleotide residues derived therefrom.

10. An isolated polynucleotide that comprises a nucleotide sequence that is complementary to the nucleotide sequence of the isolated polynucleotide according to claim 8.

11. An isolated polynucleotide that comprises a nucleotide sequence that is complementary to the nucleotide sequence of the isolated polynucleotide according to claim 9.



12. The isolated polynucleotide according to any one of claims 1 to 11 comprising DNA.
13. The isolated polynucleotide of claim 12 wherein the DNA is genomic DNA.
14. A vector comprising the isolated polynucleotide according to any one of claims 1 to 13.
15. A host cell transformed or transfected with the polynucleotide according to any one of claims 1 to 13 or the vector of claim 14.
16. The isolated polynucleotide according to any one of claims 1 to 13 in operable connection with a heterologous regulatory sequence which controls gene expression.
17. A method of producing a polynucleotide which encodes TNF- γ comprising hybridizing at least 30 contiguous nucleotides derived from SEQ ID NO:1 under stringent hybridization conditions with nucleic acid for a time and under conditions sufficient for hybridization to occur and then detecting said hybridization.
18. A method of producing a tumor necrosis factor (TNF- γ) polypeptide, said method comprising incubating or growing the host cell of claim 15 for a time and under conditions sufficient for expression of the polypeptide encoded by the introduced polynucleotide in said cell to occur.
19. A method of producing a cell capable of expressing a a tumor necrosis factor (TNF- γ) polypeptide, said method comprising transforming or transfecting a cell with the vector of claim 14.
20. A recombinant tumor necrosis factor (TNF- γ) polypeptide when produced by the method of claim 18.



21. An isolated or recombinant tumor necrosis factor (TNF- γ) polypeptide which comprises an amino acid sequence selected from the group consisting of:

- (a) amino acid sequence shown as residues -25 to 149 of SEQ ID NO:2;
- (b) amino acid residues 1 to 149 of SEQ ID NO:2;
- (c) the amino acid sequence of the full-length polypeptide encoded by the human cDNA contained in ATCC Deposit No. 75927;
- (d) the amino acid sequence of the mature polypeptide encoded by the human cDNA contained in ATCC Deposit No. 75927;
- (e) the amino acid sequence of an analogue or derivative of any one of (a) to (d) wherein said analogue or derivative is at least 70% identical to any one of (a) to (d) and has tumor necrosis factor (TNF- γ) activity; and
- (f) a fragment of any one of (a) to (d) that is encoded by at least 30 contiguous nucleotide residues present in SEQ ID NO:1 or the human cDNA contained in ATCC Deposit No. 75927 or a degenerate nucleotide sequence thereto.

22. The isolated or recombinant polypeptide of claim 21 comprising amino acid residues -25 to 149 of SEQ ID NO:2.

23. The isolated or recombinant polypeptide of claim 21 comprising amino acid residues 1 to 149 of SEQ ID NO:2.

24. The isolated or recombinant polypeptide of claim 21 comprising the amino acid sequence of the full-length polypeptide encoded by the human cDNA contained in ATCC Deposit No. 75927.

25. The isolated or recombinant polypeptide of claim 21 comprising the amino acid sequence of the mature polypeptide encoded by the human cDNA contained in ATCC Deposit No. 75927.

26. An antibody which binds specifically to the isolated or recombinant



polypeptide according to any one of claims 20 to 25.

27. A compound which antagonises the activity of the polypeptide according to any one of claims 20 to 25 or a naturally-occurring form of said polypeptide, wherein said compound was not known previously to antagonise the activity of said polypeptide.

28. A compound which agonises the activity of the polypeptide according to any one of claims 20 to 25 or a naturally-occurring form of said polypeptide, wherein said compound was not known previously to agonise the activity of said polypeptide.

29. A method of treatment of a patient having need of human TNF- γ comprising administering to the patient a therapeutically effective amount of the polypeptide according to any one of claims 20 to 25 or the compound of claim 28 or a composition comprising said polypeptide or said compound.

30. A method of treatment of a patient having need to inhibit human TNF- γ comprising administering to the patient a therapeutically effective amount of the compound according to claim 27 or a composition comprising said compound.

31. A pharmaceutical composition comprising the polypeptide according to any one of claims 20 to 25 in combination with a pharmaceutically acceptable carrier.

32. The method of claim 29 wherein the polypeptide according to any one of claims 20 to 25 or the composition comprising said polypeptide is administered by providing to the patient DNA encoding said polypeptide and expressing said polypeptide *in vivo*.

33. A method of identifying a modulator of human TNF- γ activity comprising:
(a) combining endothelial cells, Con A, [3 H]thymidine, and a compound to be tested for modulatory activity with the isolated or recombinant polypeptide according



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to any one of claims 20 to 25 for a time and under conditions sufficient for human TNF- γ activity to stimulate [3 H]thymidine incorporation into said endothelial cells; and

(b) determining the level of [3 H]thymidine incorporation in (a) compared to the [3 H]thymidine incorporation obtained in the absence of said compound, wherein a variation in [3 H]thymidine incorporation indicates that said compound is a modulator of TNF- γ activity.

34. The method of claim 33 wherein the modulator of human TNF- γ is an agonist of human TNF- γ activity.

35. The method of claim 33 wherein the modulator of human TNF- γ is an antagonist of human TNF- γ activity.

36. A compound which agonises the activity of human TNF- γ when identified by the method of claim 34, wherein said compound was not known previously to agonise TNF- γ activity.

37. A compound which antagonises the activity of human TNF- γ when identified by the method of claim 35, wherein said compound was not known previously to antagonise TNF- γ activity.

38. A method of diagnosing a disease in a subject or a susceptibility of a subject to a disease, wherein said disease is related to a mutation in the TNF- γ -encoding nucleotide sequences of said subject, and wherein said method comprises determining a mutation in a nucleotide sequence of said subject which encodes TNF- γ using the isolated polynucleotide according to any one of claims 1 to 13 or a chemically-synthesised oligonucleotide comprising an identical nucleotide sequence thereto or a vector comprising said nucleotide sequence.



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39. The method according to claim 38 wherein the mutation is determined by comparing the nucleotide sequence of the subject which encodes TNF- γ with the nucleotide sequence of the nucleotide according to any one of claims 1 to 13, and wherein a difference between said nucleotide sequences is indicative of the mutation.

40. The method according to claim 38 or 39 when used to diagnose a tumor or a susceptibility to a tumor in a subject.

41. A method of diagnosing TNF- γ expression in a subject comprising analysing a sample derived from said subject for the presence of the polypeptide according to any one of claims 20 to 25.

42. The method according to claim 41 comprising contacting a biological sample derived from said subject with an antibody molecule capable of binding to the isolated or recombinant polypeptide according to any one of claims 20 to 25 for a time and under conditions sufficient for an antigen-antibody complex to form and then detecting said complex formed.

43. A method of inhibiting tumor cell growth in a subject comprising administering to the subject a therapeutically effective amount of the polypeptide according to any one of claims 20 to 25 or the pharmaceutical composition according to claim 31 for a time and under conditions sufficient for tumor growth to be inhibited.

44. Use of the polypeptide according to any one of claims 20 to 25 in the manufacture of a medicament to inhibit tumor cell growth, induce cell adhesion or promote endothelial cell growth in a human or animal subject.

45. Use of the isolated polynucleotide according to any one of claims 1 to 13 or the vector of claim 14 in the manufacture of a medicament to inhibit tumor cell growth, induce cell adhesion or promote endothelial cell growth in a human or animal subject.



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46. The vector of claim 14 substantially as hereinbefore described with reference to the Figures and/or Examples.

47. The host cell of claim 15 substantially as hereinbefore described with reference to the Figures and/or Examples.

48. The method according to claim 18 substantially as hereinbefore described with reference to the Figures and/or Examples.

49. The method according to claim 19 substantially as hereinbefore described with reference to the Figures and/or Examples.

DATED this TWENTY FOURTH day of JUNE, 1999

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Patent Attorneys for the Applicants



AUSTRALIA

Patents Act 1990

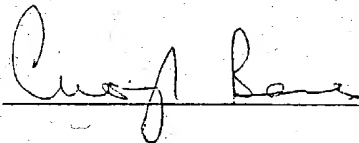
IN THE MATTER OF Australian Patent
Application Serial No. 696764 by Human
Genome Sciences, Inc.

-and-

IN THE MATTER OF Opposition thereto by
Ludwig Institute for Cancer Research

THIS IS Exhibit PAWR-4
referred to in the Statutory Declaration
of Peter Adrian Walton Rogers
made before me

DATED this 12th Day of November, 2001

A handwritten signature in cursive script, appearing to read "Craig Lane", written over a horizontal line.

(Signature of Witness)

Medical Practitioner